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THE STATUS OF CARDIAC SURGERY*

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The thought of a surgical attack on the heart organ itself has been with surgeons for centuries. Strangely enough, it was the leaders in surgery rather than the internists who held back cardiac operations. Morgagni described cardiac tamponade perfectly and Napoleon's surgeon, Larrey (1), cured such a patient with a linen drain. To such leaders, however, as Billroth, Kocher and others the heart was sacrosanct; even aspiration of the pericardium was discouraged. Trendelenberg added to cardiac surgery with his work on pulmonary embolism. In 1923 Cutler and Beck (2) accomplished the first valvulotomy by a knife, and Souttar (3) in 1925 performed a successful valve fracture digitally. World War II gave great impetus to cardiac surgery, and many foreign bodies were removed from the heart and great vessels at that time. Major cardiac operations, however, actually date from 1938, when a patent ductus was ligated by Gross (4) in the United States and by Crafoord (5) in Sweden.

The earlier surgeons were certain that the heart could not tolerate any type of manipulation. This thought was based mainly upon their experimental efforts to keep dogs' hearts beating following operation. The human heart is different. Many other parts of the body are also essential, but we are dependent upon this remarkable organ from the moment we start life until we die. An organ which has 70 to 80 beats per minute or 42 million beats per year, exerts a force of 5 to 10 tons every twenty-four hours and does this for an average of fifty to one hundred years. If we each lived the biblical three-score and ten years, our heart would pump 250 million quarts of blood and beat 3 billion times. This amount of blood would be sufficient to fill the Yale football bowl. The energy obtained from this force, if entirely expended at one time, would lift the mammoth U.S.S. Forrestal 15 feet out of the water. Thus, the human undiseased heart is a formidable organ, and even when diseased, it is a resilient one.

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The ancient investigators were well aware of the heart, and as early as Hippocrates' time from 460 to 370 B.C., the chambers, valves and vessels were well described. Erroneously, the arteries were considered to carry air and the veins blood. Galen, in 200 B.C., wrote such a good description of the heart that his interpretation of its function lasted for fourteen centuries.

With the finding in the saliva of the leech of a substance (herudin) which prevented coagulation of the blood, the possibility of anticoagulation was born. Heparin, which prevents the conversion of prothrombin to thrombin, was first prepared from liver in 1916 and purified in 1933. Thus, the clot problem in cardiac surgery was solved. In the development of cardiac surgery, blood transfusions, anticoagulants, antibiotics and anesthesia all have played a major part.

INDIRECT SURGERY OF THE HEART

Initial surgical efforts toward operating on the heart were concerned with the repair of cardiac injuries. This was followed by the development of operations on the large vessels *around* the heart. Coarctation of the aorta was successfully treated by Gross (6) and by Blalock (7) in 1944 and 1945, first with a by-pass procedure and then by excision and end-to-end anastomosis. Further experiences with by-passing operations included the Blalock-Taussig (7) operation in which the end of the subclavian artery was anastomosed to the side of the pulmonary artery in order to by-pass pulmonary stenosis. This was a great advance and overcame some of the symptoms of the cyanotic child (Fig. 1), the so-called Blue Baby. Pott's (8) ingenious operation of anastomosing the aorta to the pulmonary artery is a similar procedure. These operations create fistulas, and thus again a cardiac lesion develops. Although such procedures have been successful in relieving cyanosis, the future cardiac picture in these patients is not certain.

CLOSED SURGERY OF THE HEART

Many of the lesions which cause death from heart disease are the end-result of the scar after the disease is over. One of the greatest killers in this respect is rheumatic fever. Cardiovascular diseases account for 3 out of every 4 deaths of those patients who survive infancy. The school child, particularly, is susceptible. Approximately one sixth of our population, 26 million, are enrolled in school in any one month; one-fourth of the deaths among young people 5 to 19 years of age are from heart disease. Eighty-five per cent of the 1 million rheumatic heart patients in the United States have mitral valve lesions. Most of these valvular diseases result in death by middle age. In mitral stenosis the disease heals by scarring and fibrosis; thus the valve does not open and close well, and does not permit sufficient blood to pass through it to sustain life. Consequently, patients may die indirectly from a disease which is healed. If the mitral valve opening is large enough to admit the index finger,[1] the patient lives; but if the opening is only large enough to admit the tip of the little finger, the patient dies. Thus, a difference in size comparable to that between the tips of the index and fifth fingers may decide life or death. If the valve will not open properly, it cannot close com-

[1] Average adult male size.

FIG. 1. Tetralogy of Fallot. Typical cyanotic facies and defective growth, in a girl aged 4.

pletely; therefore relief of the stenotic lesion often relieves some of the abnormality due to insufficiency.

These findings led to the technic of *closed cardiac surgery* (Fig. 2). Such operations consisted of mitral commissurotomy or finger-fracture of the valve as we know it; mechanical dilation of the pulmonary or aortic valve through a blind approach; and the "purse string" suture or prosthetic operation, in which heart valves are closed to some extent mechanically. Replacement of the aortic valve in insufficiency (9) is also in this category. With closed heart surgery, many lesions could be corrected. Gross (10) sewed a rubber well over the atrium and let blood enter this well. He then repaired septal defects blindly through the blood in the well.

A large group of patients, however, have heart lesions which cannot be corrected by such closed methods, and these lesions often lead to the patient's untimely death. Among such abnormalities are congenital defects in the walls, the intra-atrial and intra-ventricular septal defects. In many patients with pul-

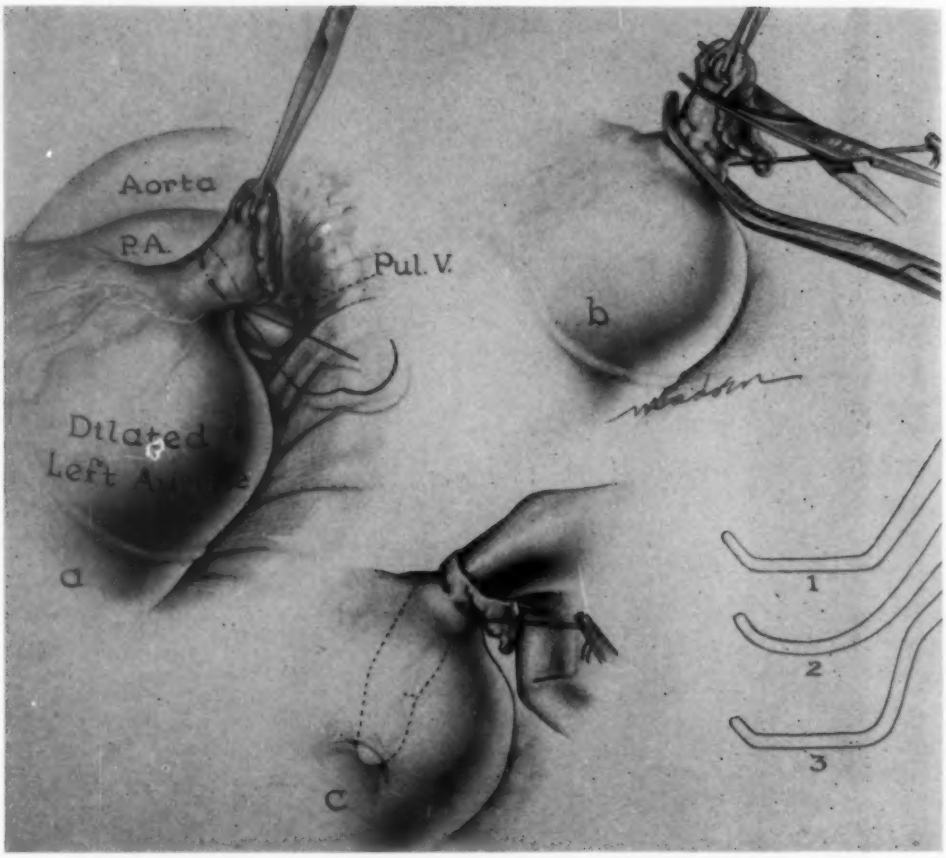

FIG. 2. Commissurotomy for mitral stenosis. In many instances, purse string suture is not required. (From Pratt, G. H.: Cardiovascular Surgery. Philadelphia, Lea & Febiger, 1954.

monary stenosis, the lesions were worse after a surgical attempt to repair them blindly than before the operation. Hypothermia, as an aid to heart surgery, then entered the picture.

OPEN SURGERY OF THE HEART, WITH HYPOTHERMIA

Normally, the arterial circulation to the brain can be shut off for three minutes without permanent damage from anoxemia; but if it be shut off for four minutes, irreversible changes in brain tissues will have occurred. This short period is the reason why so many cardiac arrests end fatally. In a like manner the cells of the heart muscle are extremely sensitive to a lack of oxygen and an increase in the concentration of carbon dioxide. Cells in the spinal cord begin to die if anoxemia persists for ten minutes. If, however, the body temperature is reduced to 31.5°C., then the circulation to the brain can be shut off for as long as seven to eight minutes without serious damage. The circulation to the spinal cord can be shut off for at least an hour at that temperature without irreversible changes. Below a temperature of 31.5°C. however, the heart cells become sensitized, and ventricular fibrillation, often a fatal lesion, is liable to develop.

With the advent of hypothermia, open surgical operations on the heart became possible. The cardiac intake and outflow of blood could be shut off for from seven to nine minutes. If one could open the heart, repair the defect, and close the heart within these seven to nine minutes, many congenital cardiac defects could be corrected. Thus, open heart surgery was developed, but it was definitely restricted by considerations of time (11, 12). Many cardiac lesions were corrected in this manner, but often the time limitation led to hurried and inaccurate or incomplete surgical repair.

OPEN SURGERY OF THE HEART COMBINED WITH AN EXTRACORPOREAL CIRCULATION SYSTEM

The idea of a mechanical by-pass in which a machine would be substituted for both the heart and lungs had been tried for a long time. I do not intend to discuss the concepts of the various cardiac machines, such as that of Gallois, of Lindbergh, of Carrel, and of Dodrill *et al.* (13, 14), except to say that the progress was slow, difficult and frequently delayed. It is important to understand that the cause of this delay was not merely that the principle on which this work was based was in error; the delay was chiefly due to the difficulty in obtaining surviving subjects among the dogs used in the experiments. It was not clear to the investigators whether the deaths were due to a fault in the mechanics of the heart-lung machine, or to atelectasis, hemolysis, air bubbles and other pathologic states which followed the by-pass operations on animals.

Gibbon (14), a pioneer, spent many years and large amounts of money in this work. His protocol was based on the premise that all the blood in the body must be oxygenated in any by-pass pump. An experiment by Andreason and Watson

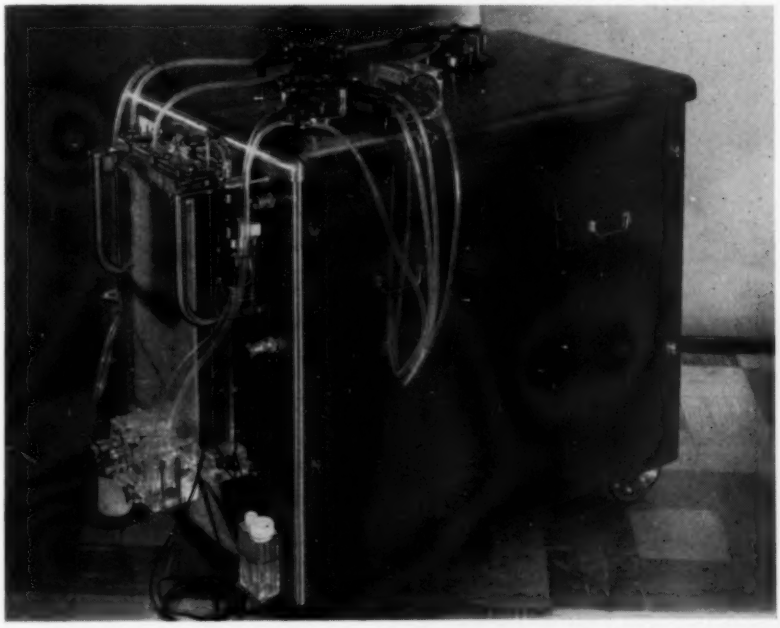

FIG. 3. Gibbon type of extracorporeal circulation apparatus. All of blood is oxygenated.

(15) in England changed this concept and gave rise to the azygos principle. This experiment showed that when both the superior vena cava and the inferior vena cava of a dog were occluded, the dog could live for forty-five to fifty minutes. This meant that only the blood brought to the lungs by way of the azygos vein (one-seventh of the blood supply) was being oxygenated. Thus, it was shown that one could by-pass the heart and lungs and oxygenate only part of the blood in the resting state and still have a living subject. This procedure also involved a definite time limit, but one which was much greater than that imposed by hypothermia. At present we have two heart-lung by-pass systems available for open heart surgery. The Gibbon type is one in which all of the blood is removed and oxygenated (Fig. 3). It is in clinical use at the Mayo Clinic, in Philadelphia and elsewhere. The DeWall-Lillehei type (16, 17) is a partial blood oxygenator and is exemplified by the University of Minnesota bubble pump oxygenator, in which only a portion of the blood is removed and oxygenated (Fig. 4). With the latter system, under resting conditions, 35 cc. of blood per kilogram of body weight per minute must be oxygenated. Most of the pumps of this type oxygenate 60 cc. of blood per minute per kilogram of body weight.

Thus evolved the principle of open surgery of the heart. Its possibilities are unlimited. Both the right and left heart can be opened—the latter with due care to avoid an air embolus to the brain. Lesions which were previously corrected by operations of the blind type (involving fracturing of tissues digitally or by jabbing with instruments) can now be operated on in an open, dry cardiac field by an unhurried technic. Many aortic lesions also can be corrected.

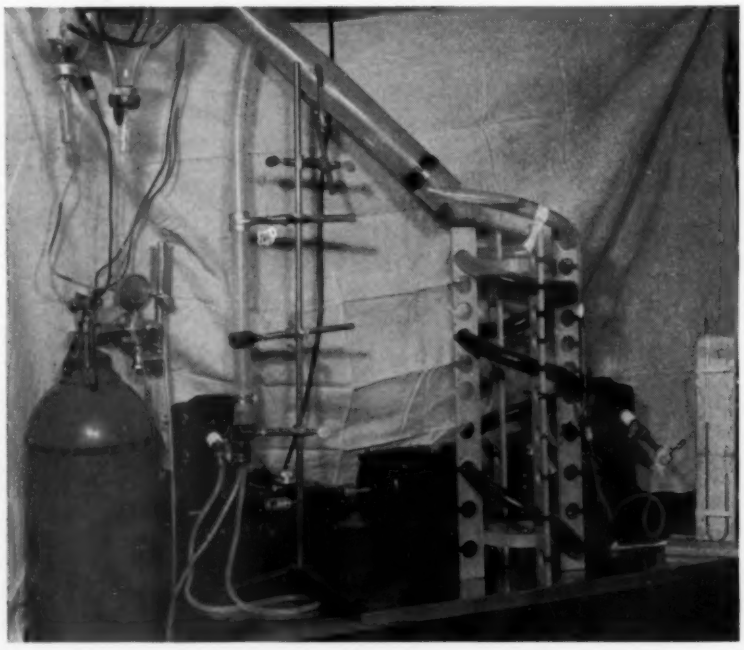

FIG. 4. Bubble pump oxygenator for partial by-pass of the circulation. Modified from apparatus used at University of Minnesota.

OPEN SURGERY COMBINED WITH STOPPAGE OF THE HEART

For purposes of operation, the heart can also be stopped for as long as one hour. This adds quiet heart to dry, open field. The heart may be stopped by a chemical such as the potassium ion in its chloride or citrate form, acetylcholine, or an electric shock. Thus, the surgeon can perform the necessary surgery at his own optimal speed of operating. To stop the heart chemically, one must clamp the aorta while using the pump oxygenator to bypass the heart and lung. Potassium citrate (2 per cent solution) is injected into the blood proximally to the aortic clamp, so that it enters the coronary circulation; this stops the heart beat completely. When the clamp is removed from the aorta after the operation is completed, the blood flows through the coronary arteries and removes the potassium ion. This maneuver starts the heart beat spontaneously. At this point, ventricular fibrillation occurs in about 25 per cent of patients. To correct the fibrillation, the heart must be stopped by an electric shock and then massaged manually; at times drugs are employed to help the heart muscle resume its beat. The use of

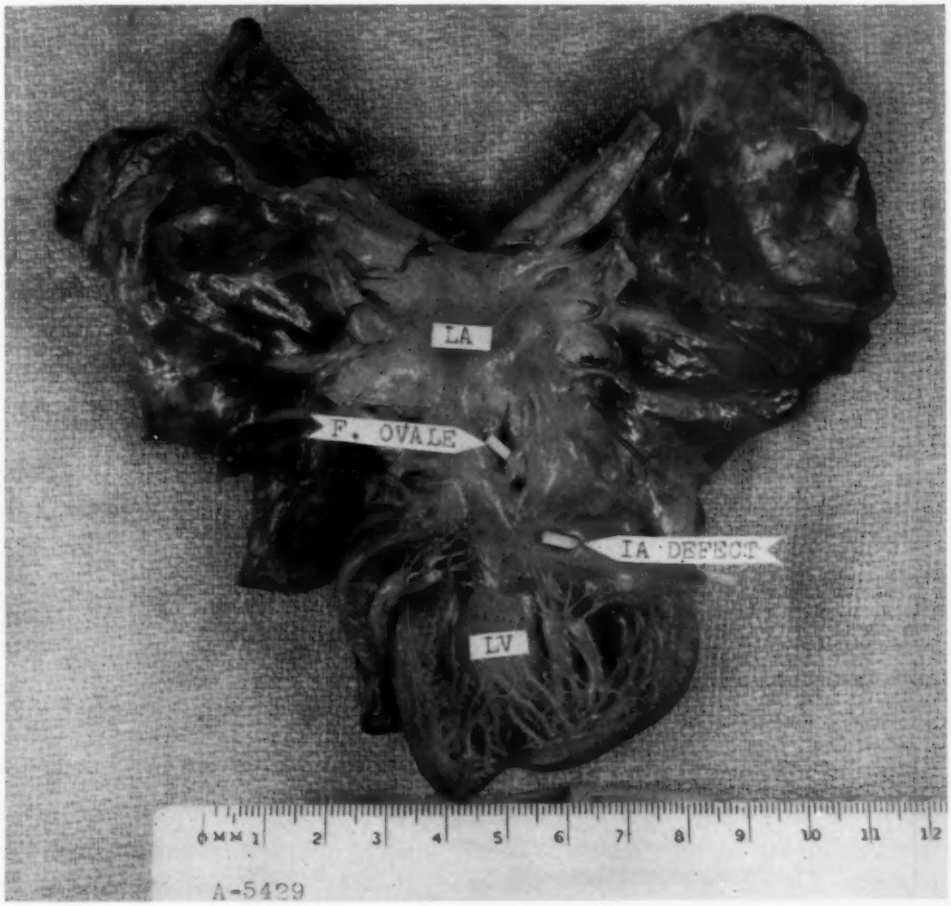

FIG. 5. Patent foramen intra-atrial septal defect. This can be repaired under conditions of extracorporeal circulation.

induced ventricular fibrillation in open surgery of the heart is a dangerous method in our experience.

Open cardiac surgery is no longer a technic of the future. It is our belief that in time it will replace medical therapy, except in congenital and acquired heart lesions (Fig. 5), in which the risk of cardiac surgery is too great, and in the more advanced lesions for which the patient consults the internist too late for beneficial surgical measures. Since half of the congenital heart lesions (50,000) which are seen in the United States each year can be operated on only with the use of an extracorporeal circulation, one realizes the great field which has opened in this work. Approximately 35,000 mitral-valve lesions develop each year, and therapy will be expedited by open cardiac surgery. The aortic valve can be openly treated also.

CORONARY OCCLUSION

The most important cardiac lesions that remain to be corrected surgically are those involving the coronary artery. With the use of extracorporeal circulation one can expect that a direct attack on these lesions may be successful. An arterial thrombectomy or graft is possible.

In the meantime, certain procedures have been developed to aid surgically the patient with the coronary syndrome.

Beck (18, 19) worked for many years on a treatment for coronary thrombosis and occlusion. The first Beck operation consisted of induction of adhesions between the pericardium and the heart muscle. Circulatory improvement often follows the formation of such adhesions in the coronary circulation. To this operation Beck added partial occlusion of the coronary sinus. In our experience, the latter addition increased the risk of the operation, and we have used the so-called poudrage procedure—the application of asbestos or talc on the cardiac surface. Beck's efforts to reverse the circulation by connecting the aorta to the coronary sinus (which he called the Beck II operation) is not in general use. Vineberg (20) inserted the internal mammary artery or one of the intercostal arteries directly into the heart muscle and reported considerable improvement in a certain percentage of his patients. More recently, Glover (21) revived an old operation of the Italians in which the internal mammary arteries were ligated on both sides at the second interspace. Without question, such an operation does cause an increased flow of blood to the pericardium, as we have demonstrated by injection studies of these mammary arteries in postmortem patients. We are unable to say whether or not the favorable result is due to a direct connection with the coronary artery, but every patient on whom we have performed this operation has been improved remarkably.

PERICARDITIS

One cardiac disorder amenable to surgery and to no other treatment is chronic constrictive pericarditis (Fig. 6). Too often it is not diagnosed correctly. The diagnostic triad of pericarditis should be thought of in any patient with intractable heart failure. This triad consists of high venous pressure, a quiet heart and,

FIG. 6. Massive pericarditis with intractable heart failure. Pericardiectomy resulted in cure.

in the acute stage, low arterial pressure (ascites in the chronic stage). The relief obtained from pericardiectomy frequently is dramatic. These patients are in a state of constant heart failure due to tamponade. They should be given the benefit of a trial with surgery, as the outlook otherwise is hopeless.

SUMMARY

The development of cardiac surgery is traced through the stages of: 1) indirect by-pass operations, 2) closed operations, 3) open operations with hypothermia, 4) open operations with an extracorporeal circulation system, and 5) open operations with stoppage of the heart. Application of surgical principles to coronary occlusion and pericarditis is discussed.

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FROM SNAKE ROOT TO SEROTONIN*

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SNAKE ROOT—RAUWOLFIA SERPENTINA

Rauwolfia serpentina, an erect, attractive bush with shiny green leaves and white or pinkish flowers, literally covers the foothills of certain parts of India. It has a long tapering, crooked root, popularly called "snake root," which contains most of the medicinal properties of the plant. For centuries this root was gathered by the natives of India, who pounded it into a powder to treat a number of illnesses including fevers, snake bite, dysentery, insomnia, nervousness and insanity. However it was not until relatively recently that Indian doctors working with mental patients observed that Rauwolfia often produced a lowering of blood pressure and a slowing of the pulse rate.

In 1949 Rustom Jal Vakil of Bombay reported on the use of Rauwolfia for the treatment of hypertension. His article, which appeared in the British Heart Journal (1), immediately attracted our attention. Using Serpina tablets, which we obtained from the Himalaya Drug Company in Bombay,[1] we were able to confirm Vakil's finding that Rauwolfia causes a moderate lowering of blood pressure in about 40 per cent of uncomplicated cases of hypertension (2–4). It also produces bradycardia and, as Vakil found, has a favorable effect on "hypertensive" symptoms. Patients usually state that they are much less nervous and irritable when taking the drug and often say that they are relieved completely of headache, dizziness and fatigue. In addition we found that Rauwolfia causes nasal congestion, a gain in weight, and increased motility of the bowel. In excessive dosage it can produce diarrhea, nightmares, or a state of agitated depression, all of which may be relieved by interrupting or reducing the dosage of the drug. At no time did we observe the development of tolerance or of addiction to the drug.

We discovered that Rauwolfia is particularly useful as an adjunct or background agent when given in combination with the more potent hypotensive drugs, particularly Veratrum, hydralazine, or hexamethonium. Rauwolfia is well tolerated over long periods of time and is essentially free of toxic or serious side-effects when given in the limited dosage that we use for the treatment of hypertensive patients. Therefore, we have recommended it as the first agent to try when instituting medicinal treatment for hypertension, and the last agent to omit from such a regimen. Indeed we usually maintain our hypertensive patients

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[1] Through the courtesy of E. R. Squibb & Sons.

on minimal doses of Rauwolfia even after the pressure has been kept at a normal level for a considerable period of time. To omit the drug in such cases almost invariably permits the pressure to rise again.

These results have been detailed fully by us and have been amply confirmed by many other workers and numerous reports in the literature. Indeed it has been most gratifying that as we have gained further experience in the use of the Rauwolfia preparations for hypertension we have had to change our clinical impressions very little from those noted in our original reports.

Early in this experience with Rauwolfia, I came to appreciate the remarkable effect that this drug may have on the personality of many patients. This was noticed not only by the patients themselves but was obvious to me from their behavior. They frequently stated that they felt much more "like themselves," or at least like the persons they wished to be. They were much less irritable, little things no longer bothered them and they could accept themselves, their lives, their families and their fellow workers with greater equanimity. These improvements in personality and changes in reactivity were so striking that I told many of my psychiatrist friends, "Rauwolfia is good psychotherapy in pill form. At least it helps me with my admittedly superficial attempts at psychotherapy in these patients" (5). I tried to get several of these friends to try the drug in psychiatrically disturbed patients. I am sorry to say that at first I did not have much success.

This did not prevent my talking about the mental effects of Rauwolfia at every opportunity. One evening when discussing this subject with Dr. Geoffrey Rake, who incidentally had also talked with psychiatrists in India about it, he asked, "You mean it makes them tranquil?" "Exactly," I replied. "It tranquilizes them," he continued. "Then it is a tranquilizer?" "Say," he then asked, "Why isn't that a good term—tranquilizer?" I don't know whether Dr. Rake is proud of it, or will even *admit* it today, but to my knowledge he was the first to use the term "tranquilizer" as it is now applied to the Rauwolfia derivatives and the other so-called "ataraxic" drugs.

Our finding that Rauwolfia was particularly effective as a hypotensive agent when used in combination with hydralazine perhaps helped to stimulate our friends at Ciba to dust off some work that they had laid aside some years before on the alkaloidal derivatives of the crude drug. Dr. Schlittler had started this work in Switzerland and soon was able to prepare a pure sedative derivative of Rauwolfia which he called reserpine (6). Shortly afterwards he came to this country and he and his associates worked out the structural formula of reserpine (7, 8). We were the first to try reserpine clinically (9, 10), and it seems remarkable in retrospect that this trial retraced almost exactly our experience with crude Rauwolfia. I refer here to the slowness of the onset of the action of both of these agents. When either drug was given to hypertensive patients in the usual effective dosage, even parenterally, nothing happened for three to four days. Then there was a slow onset of its effects in calming the nervous symptoms, slowing the heart rate, and lowering the blood pressure. These reached their peak only after several weeks or even a month or two of continued therapy.

This slowness of action of the Rauwolfia drugs suggested that they might work through some intermediate mechanism such as a hormonal or other secondary pathway. An obvious mechanism to be explored was the adrenal gland, which is known to be concerned in several different kinds of hypertension (5). However, preliminary explorations of this possibility revealed nothing of significance.

When the chemical structure of reserpine became known it was found to resemble that of yohimbine and to a lesser extent harmine, lysergic acid, and mescaline, all of which are known to have more or less exotic effects on the central nervous system. This suggested that the central nervous effects of reserpine might be related in some way to a chemical structure or property which it has in common with these other agents. One basis for chemical kinship was found to exist in the indole nucleus common to them all. This was pointed out by Hoffer and his associates in a report on the hallucinogenic effects of adrenochrome, which also contains the indole nucleus (11).

SEROTONIN

In the meantime Dr. D. W. Woolley of the Rockefeller Institute had been working on another substance, 5-hydroxytryptamine, called 5-HT or serotonin, which had been described previously by Erspamer (12) and by Page (13) and was also known to be an indole derivative. Dr. Woolley had produced a number of structural analogs of serotonin and had demonstrated that they were pharmacologically antagonistic to serotonin and therefore could be called "antimetabolites" of serotonin (14). He had further showed that yohimbine is also a serotonin antimetabolite (15). Dr. Woolley wrote to us calling our attention to his papers on this subject and expressing the opinion that reserpine also might be an antimetabolite of serotonin since it too contained the indole nucleus.

This chain of events set us upon an entirely new line of investigation with serotonin and antiserotonins, especially in hypertension. Several antiserotonins were assayed by us in man as antagonists to the actions of serotonin (16). Suffice it to say, only one, the benzyl analog of serotonin (BAS) prepared by Dr. Woolley, was suitable for being used freely in man, either intravenously or orally.

When serotonin is administered intravenously it causes intense venospasm, so that it cannot be given in sizable amounts by intravenous infusion. However, it can be given in single quick intravenous doses of about 1 mg., following which its physiologic effects can be measured in the cardiovascular, respiratory, renal and gastro-intestinal systems (17).

The effects on blood pressure of 1-mg. intravenous doses of serotonin are variable and in any case not marked. Characteristically there is an initial depression of blood pressure followed by a moderate hypertension. The pulse rate is accelerated. Respiration is also increased, concomitant with an elevation of the mid-position of the chest and hyperpnea, usually after an initial gasp or apneic period. These cardiovascular and respiratory effects are associated with distressful subjective sensations of tingling or prickling of the skin, apprehension, and sometimes substernal oppression. All of these actions can be inhibited by prior treatment with 50 mg. of BAS intravenously.

Thus we were able to demonstrate by these tests that BAS can be characterized as an antiserotonin in man as well as in animals. In some cases, but not all, intravenous BAS completely abolished the pressor effect of serotonin (though it did not materially affect the initial depressor phase). In most cases it also abolished the hyperpnea. The blockade of both effects was relative, since it could be broken by increasing the dose of serotonin. However, even when intravenous BAS did not block the pressor and hyperpneic effects of serotonin it usually abolished the unpleasant symptoms produced by intravenous administration of this drug.

When administered orally over long periods of time to hypertensive patients, BAS also had some very interesting actions (18). In about 25 per cent of patients it was definitely hypotensive, lowering the blood pressure moderately. Even more distinctive were its side-effects, which resembled remarkably those of reserpine. These included sedation, bradycardia, abdominal cramps, and nasal stuffiness. The sedative effect of BAS was its most prominent action and limited the dosage fairly sharply to about 100 mg. a day. However, in a few patients this effect (or something like it) was of remarkable benefit. I refer particularly to patients with insomnia who were able to sleep well at night only when taking BAS, and yet were fully awake during the daytime.

BAS, therefore, seemed definitely to qualify as "a tranquilizer." It was significant to us that BAS, the first clinically useful hypotensive or tranquilizing agent to be synthesized because of theoretical rather than empirical considerations, turned out to be remarkably similar in action to reserpine (though much simpler chemically). Indeed this similarity of its action to that of reserpine gave added weight to the idea that reserpine itself might exert its effect through altering serotonin or its effects in the body. Further evidence on this point became available from another source.

Serotonin was known to exist in three principal areas in the body: 1) the platelets of the blood, 2) the gastro-intestinal tract, and 3) the brain. Its presence in platelets was assumed to be related to its vasospastic quality, and thus to contribute to the styptic power of the platelets. Its presence in the gastro-intestinal tract was supposed to be related to a tonic gastro-intestinal property, since serotonin is known to be a strong constrictor of smooth muscle. However, its presence in the brain was a mystery. Dr. Woolley and others had hypothesized that serotonin might be concerned in some way with central neurotransmission or brain function and had even suggested that malfunction of the brain or insanity might be associated with a disturbance of serotonin metabolism.

Direct evidence was brought to bear on these points by Dr. Brodie and his co-workers at the National Heart Institute, who showed that reserpine depletes the entire body, including the brain, of serotonin (19). They also showed that the clinical sedative effect of reserpine is co-existent in time with its serotonin-depleting effect in the brain (which may persist for some time after a reserpine dosage) rather than with the actual presence of reserpine in the brain. Dr. Brodie further showed that an optical isomer of reserpine, similar in every other way chemically to ordinary reserpine, had neither a sedative effect nor serotonin-depleting effect. Thus it would appear that the sedative effect of reserpine may

indeed be mediated through the secondary route of the serotonin-depleting mechanism.

When BAS was given to hypertensive patients orally for the treatment of hypertension we found that there might be a moderate decline in the blood pressure during therapy with either BAS alone or BAS in combination with other hypotensive drugs. However, we were not able to demonstrate that when the drug was given orally in this way its actions were definitely those of an antiserotonin, as measured by the pressor or respiratory reactions to serotonin (18). This might be explained by the fact that we were not able to give BAS orally in sufficiently large or prolonged dosage to demonstrate its antiserotonin effects by these methods. The latter possibility was supported by the observation that prolonged oral administration of BAS did greatly lessen the symptoms produced by intravenous doses of serotonin. Similarly, in patients with carcinoid (a tumor which is known to release large amounts of serotonin into the blood stream, causing severe symptoms), oral BAS definitely decreased the symptoms of the disease. It is interesting that reserpine also decreased the symptoms of carcinoid, thus giving additional support to the idea that it, too, may be an antiserotonin physiologically (18).

COMMENT

We have come quite a distance from snake root and reserpine, to serotonin and the antiserotonins. Nevertheless the road seems to have been a fairly straight one, and even the path ahead to be clearly indicated, at least in part. Thus, it is logical to believe that other chemical analogs of serotonin will soon be found which will be more effective as antiserotonins and perhaps more useful clinically. They should also be more specific in their beneficial effects, *i.e.*, they should act on the central nervous system alone, or on the blood pressure alone or, when necessary, should exert a combination of these two actions. The results so far are neither ideal nor final. Their significance is much greater in pointing the way to, rather than in ending the search for, better antihypertensive and better tranquilizing drugs. Although snake root and serotonin have already taught us much, they may teach us more by helping us to understand the chemical nature of hypertension and of mental disease.

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HORMONAL THERAPY VERSUS WATCHFUL WAITING IN HYPOGONADISM: THE MALE*

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An important decision which must often be made by a clinician is whether to leave cases of juvenile hypogonadism untreated awaiting spontaneous puberty, or to institute hormonal therapy. If the decision is in favor of hormonal therapy, at what age should it be started, and in what form? The problem revolves around the possibility that administration of hormones may cause too rapid or too premature an acceleration of sexual development and thereby bring about some associated undesirable effects through the action of the selected therapy upon organ systems other than the gonads. In addition to the choice of the appropriate form of therapy, the optimal time for institution of endocrine treatment requires the expert judgment of the physician. Therapy, when appropriately administered, may insure adequate sexual development so that the hypogonadal male can be prepared to achieve his birth-right of procreation and marital bliss more effectively. It is this therapeutic approach and the appropriate time for administration with which we are concerned in the present discussion.

The young hypogonadal male often seeks the advice of a physician because of the worry and concern of his parents, particularly in his pre-adolescent years. If a boy reaches a stage of life in which his confreres are considerably better endowed than he with respect to their genitalia, and he becomes aware of his insufficiencies, subconscious anxiety and an abnormal behavior pattern may develop. Feelings of inferiority often appear earlier in the hypogonadal male than in the similarly affected female. They are accentuated by the fact that the genitalia and gonads are primarily external, in contrast to those of the hypogonadal female in whom, despite an infantile uterus, there is no corresponding immature appearance of the external genitalia. The male with an infantile penis may be ridiculed by his associates, especially among any group of children using common bathing facilities, and this may take place as early as 6 to 8 years of age. The ridicule the patient is compelled to face can create an important psychologic problem, which in itself evokes the need for therapy. Inasmuch as the penis is dependent upon the testes for its growth and develpment, one must consider the functional state of the testes in the male with hypogonadism. Similarly, since the testes are dependent upon the pituitary for their sustenance, one must consider the pituitary. The problem then becomes a complex one, as it is necessary to distinguish between delayed puberty, testicular insufficiency, and gonadotropic insufficiency. The picture becomes even more complex, however, when we realize

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the pituitary, although the "master gland" of the endocrine system, is, like all dictators, dependent upon its subjects for control. Thus, the thyroid gland and the adrenals may also be important factors in determining the integrity and function of the pituitary gland. An abnormality of thyroid function may induce sufficient alteration of the pituitary to cause decreased gonadotropic secretion, with resultant subminimal stimulation of the testes, and secondary inadequate penile development. The decision, then, with respect to therapy is governed by the judgment of the physician not only as to the time of initiation but as to the type which would be most appropriate. Thus, an adequate diagnostic appraisal must be made before remedial therapy can be instituted.

CLINICAL APPRAISAL OF HYPOGONADISM

In the clinical evaluation of a patient suspected of hypogonadism one must first establish the fact that hypogonadism is present. This involves physical examination, and a comparison of genital size and body development in the patient with those in a normal boy of the same age and build. If these clinical criteria indicate hypogonadism, the child should be subjected to further diagnostic work-up.

Thyroid factor

Thyroid function must be evaluated, using as many parameters as may be convenient. As a minimum, these should include determinations of the serum

FIG. 1. G. B., aged 7½ years. Hypogonadal male, moderately obese, with evidence of hypothyroidism. Excellent response to chorionic gonadotropin therapy.

level of protein-bound iodine and cholesterol, and a glucose tolerance test. The purpose of these tests is not only to determine whether hypothyroidism is present, but to ascertain the presence or absence of the hypometabolic syndrome. The latter is believed to be due to an inability of the tissue to de-iodinate thyroxine into triiodothyronine, the form in which thyroid hormone is utilized at the cellular level. Hence, a patient may have a normal level of circulating thyroxine (normal PBI) and still have thyroid deficiency in the peripheral tissues. The protein-bound iodine test provides a measure of the circulating thyroid hormone, but does not provide an index of the amount of utilizable thyroid hormone in the tissues. Determinations of glucose tolerance and of the serum cholesterol level supply these data, to some degree. It is possible to have a dichotomy of results—a normal level of serum protein-bound iodine associated with an elevated level of serum cholesterol and a flat glucose tolerance curve (increased tolerance). This is in contrast to the situation in frank hypothyroidism, in which the concentration of serum protein-bound iodine is low, that of cholesterol is high, and glucose tolerance is increased. In addition to the foregoing diagnostic procedures, a roentgenographic (not fluoroscopic) evaluation of bone age, will furnish pertinent

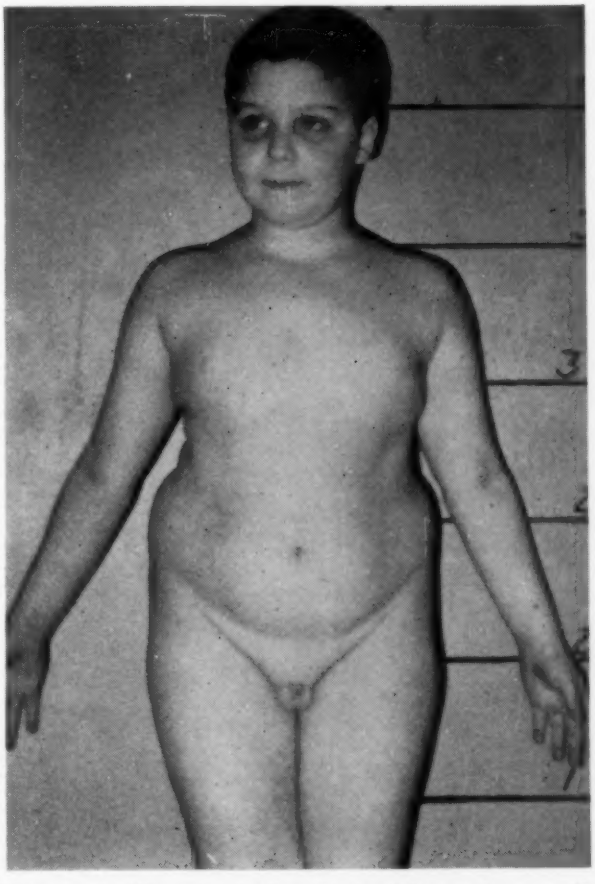

FIG. 2. R. P., aged 8 years. Hypogonadal male requiring and responding well to chorionic gonadotropin therapy.

information as to the thyroid status. Retardation of bone age (using the more modern standards for bone development) may provide an important clue in the diagnosis of both hypothyroidism and the hypometabolic syndrome. With correction of the hypothyroid or hypometabolic condition, normal gonadal development may ensue.

In addition to the laboratory findings, there are certain specific clinical findings that one should always look for in the patient with either hypothyroidism or the hypometabolic syndrome. These may be grouped as follows: dryness of the skin, particularly on the extensor surfaces of the body, associated with a tendency towards dryness of the scalp; and increase of lanugo-like hair on the dorsal areas; a tendency towards constipation; intolerance to cold; and a general sluggishness in both thought and action.

The therapeutic approach to the patient with hypothyroidism is the administration of thyroid hormone, either in the form of U.S.P. thyroid, thyroglobulin, sodium-L-thyroxine or *l*-triiodothyronine. Thyroid and thyroglobulin are administered in comparable doses. Sodium-L-thyroxine and *l*-triiodothyronine (liothyronine) are crystalline compounds which offer the physician a more precise and exact dosage with a greater predictability of effect. Equivalent dosages of these various compounds are as follows: 100 mg. of thyroid = 100 mg. of thyroglobulin = 0.3 mg. of sodium-L-thyroxine = 0.1 mg. of *l*-triiodothyronine. The effects of the first three preparations are comparable with respect to onset and duration; in routine dosages, all three drugs take approximately two to three weeks to achieve their full therapeutic effect and a comparable period of time is

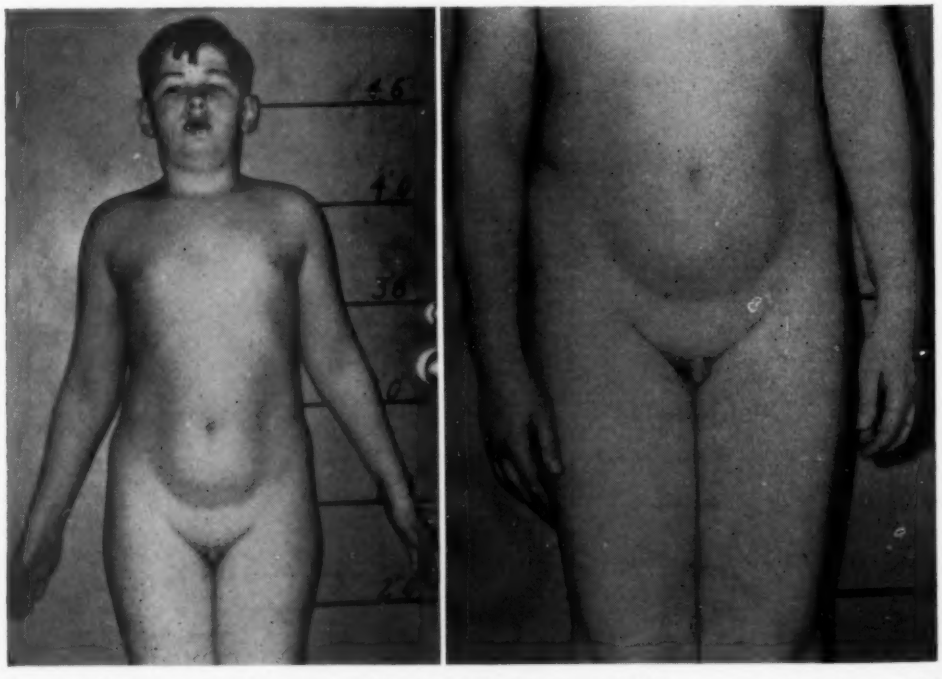

FIG. 3. M. G., aged 11 years, and only 57½ inches tall. Hypogonadal male requiring chorionic gonadotropin. Response was adequate with respect to both growth and genital development.

required for complete dissipation of effect. Triiodothyronine has the advantage of taking only two to three days to achieve an effect that requires two to three weeks with the other drugs. It would appear to provide rational replacement therapy in the hypometabolic syndrome.

Occasionally in children sodium-L-thyroxine and triiodothyronine have been noted to be synergistic in effect, so that the therapeutic response to a combination of these preparations is better than that to either drug alone. The use of any one of the four thyroid preparations in hypothyroidism, or of triiodothyronine in the hypometabolic syndrome, tends to lower the level of blood cholesterol, induce a more normal type of glucose tolerance curve, and accelerate the bone age towards the normal. An improvement in hypogonadism has also been noted in these patients.

Hyperthyroidism may be categorically dismissed as a factor in hypogonadism. Even when of a mild nature and difficult to recognize clinically, it is never of importance in adolescent hypogonadism in the adolescent. Severe hyperthyroidism in the young demands adequate and prompt therapy, not because of hypogonadism, but because of the precarious general condition of the patient.

Pituitary-gonadal system

Having established the euthyroid state, either endogenously or by the exogenous administration of one of the appropriate thyroid preparations, one must then determine the functional activity of the pituitary-gonadal system. The clini-

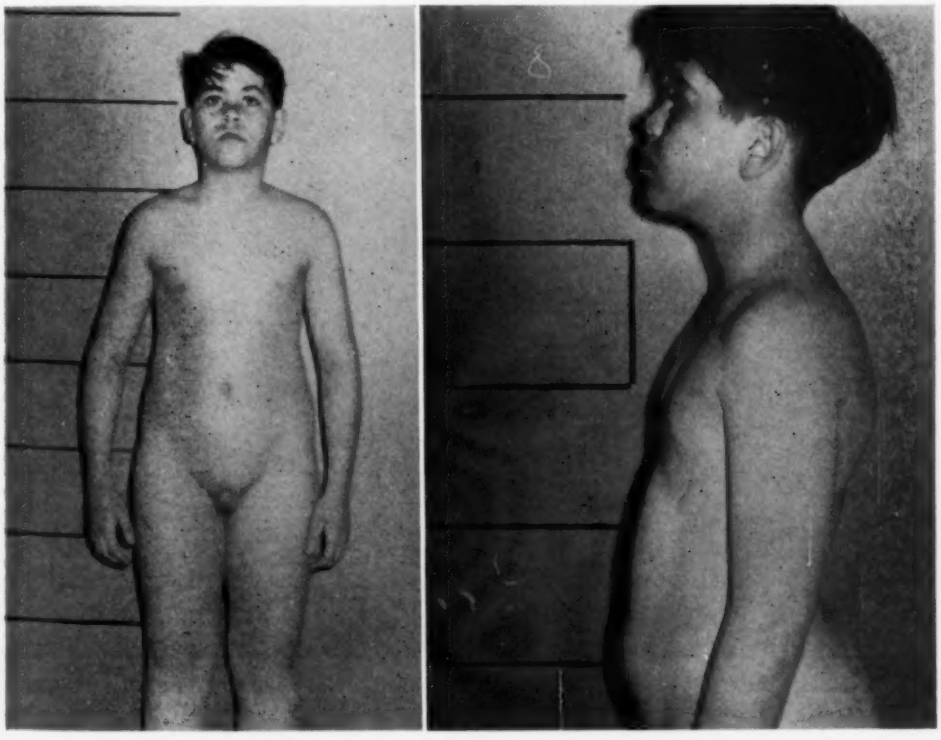

FIG. 4. M. E., aged 14 years; height only 57½ inches. Hypogonadal male whose response to chorionic gonadotropin was not as marked as that noted in the younger children.

cal findings of hypogonadism in the euthyroid patient are apparent and are characterized by failure of development of secondary sex hair, associated with hypoplastic genitalia. Confirmation of the clinical impression must be established by adequate laboratory criteria. The laboratory test most helpful for this appraisal is the 17-ketosteroid determination. Normally, the excretion of 17-ketosteroids is approximately 1 mg. per twenty-four hours per year of life, the normal range for the adult male being between 10 and 24 mg. per twenty-four hours. The 17-ketosteroid excretion is a rough index of whether or not the testes of the child are secreting an adequate amount of gonadal hormone. If a low excretion is found, with or without retardation of bone age, the patient is a candidate for gonadal stimulation with the appropriate hormone for correction of the hypogonadal state.

HORMONAL THERAPY VERSUS WATCHFUL WAITING

A delay in therapy in such a child may result in failure of gonadal development. Some clinicians believe that retardation of puberty in these cases may be present normally, and that the withholding of therapy will not cause any irreparable harm. Whether or not such children may be examples of delayed puberty and may undergo adequate development at a later time is not germane to this discussion. We feel that hypogonadism in childhood, when diagnosed by both clinical and laboratory criteria, necessitates the institution of therapy to prevent psychologic aberrations and to permit more nearly normal psychosexual

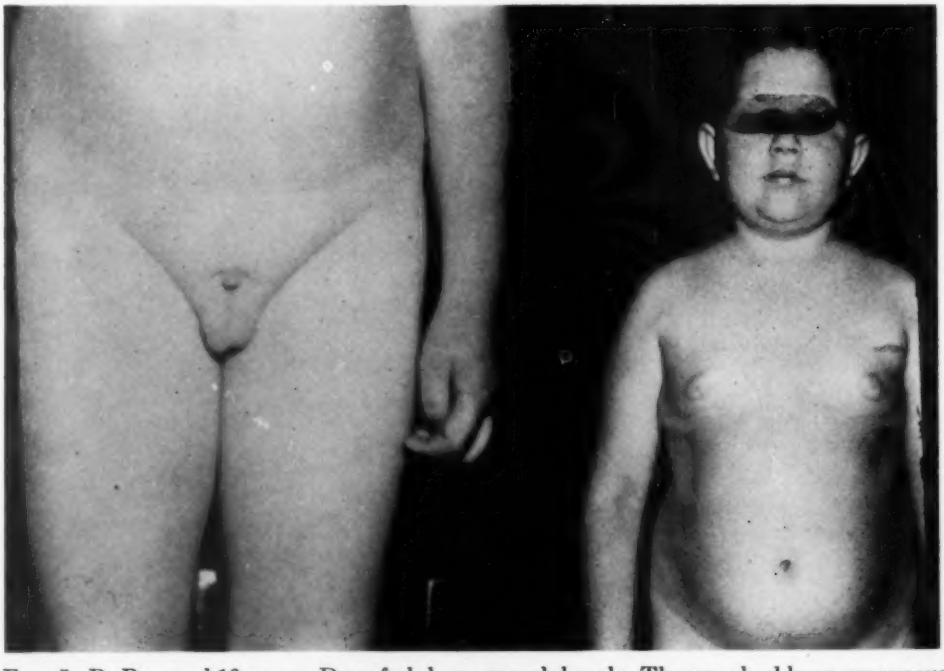

FIG. 5. R. B., aged 16 years. Dwarfed, hypogonadal male. Therapy had been erroneously withheld, to await spontaneous development. Patient had all the manifestations of hypopituitarism.

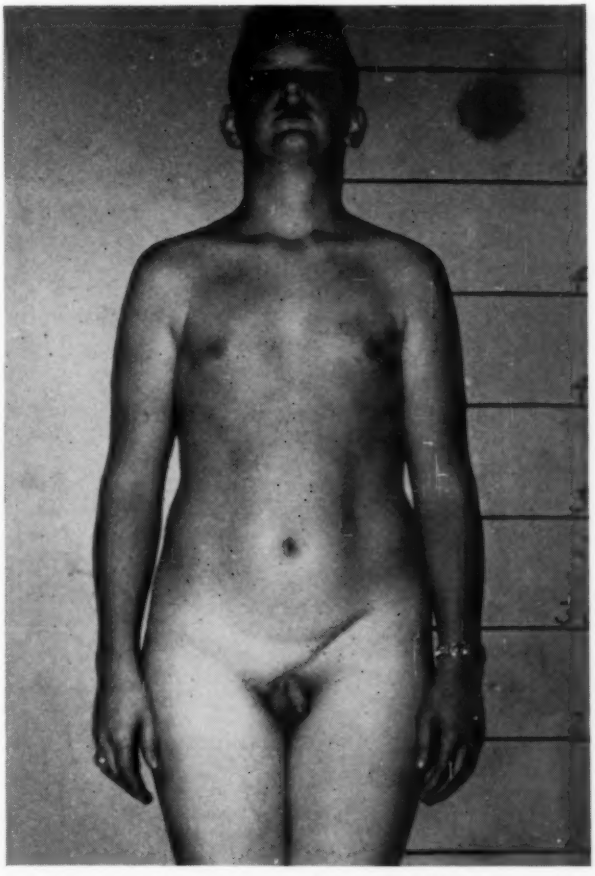

FIG. 6A. J. C., aged 18 years. Hypogonadal male with open epiphyses. Response to chorionic gonadotropin therapy was excellent.

development. How long should one await spontaneous but delayed puberty before initiating hormonal therapy? Figures 1–8 portray hypogonadism in males ranging in age from 7½ to 33 years. The question arises as to the appropriate age at which therapy should be started; is it 8, 10, 14 or 18 years—or even 30 years in adults? The patients in Figures 1–8 are candidates for chorionic gonadotropin therapy. The pertinent clinical data on each patient are included in the figure legends and need little further comment.

Several of these patients serve to emphasize the plea being made in this report against watchful waiting. Patient R. B. (Fig. 5) was a 16-year-old boy, short in stature, with marked hypogonadism, who had the laboratory and clinical stigmata of hypopituitarism. He had been denied gonadal stimulation therapy by the referring physician because of the latter's conservatism. However, the epiphyses were open; this indicated that if hormones were administered some gonadal response could still be achieved. Patient S. K., aged 32 years (Fig. 7A), represents an extreme result of watchful waiting. Fortunately at this late age his epiphyses were still open (Fig. 7B) so that, as anticipated, initiation of hormonal therapy resulted in some growth of the penis, increase in libido, and

FIG. 6B. Note the open epiphyses of the phalanges, metacarpals and distal portions of the radii and ulnae in this patient. Usually these epiphyses would be closed at this age. (Patient J. C., aged 18 yrs.)

awakening of potentia; in addition, there was an increase in testicular size as well as an increase in muscular mass and strength. On the other hand, Patient S. R. (Figs. 8A and 8B), who was the same age as S. K. and also a victim of watchful waiting, failed to respond to intensive hormonal therapy; massive doses failed to enhance penile growth or alter his eunuchoidal appearance. It should be noted that the epiphyses of this patient were closed. In J. C. (Fig. 6), an 18-year-old hypogonadal male with open epiphyses (Fig. 6B) and a tendency towards a eunuchoidal build, there was a dramatic response to chorionic gonadotropin and androgen therapy. Watchful waiting, if it had been prolonged for several more years, would almost certainly have led to a less dramatic result, particularly if the epiphyses had closed in the interim. The later therapy is instituted, the less the response. One should be aware that irreversible hypogonadism may result if treatment is delayed until after the epiphyses are closed. It is our opinion that if a child of 8 shows evidence of frank hypogonadism, hormonal therapy is indicated at that time. If hypogonadism is detected at the age of 10 or 12 years, therapy should be started at that time. Delay of endocrine treatment until the age of 18, 20 or 30 years will often result in a poor response in the patient who

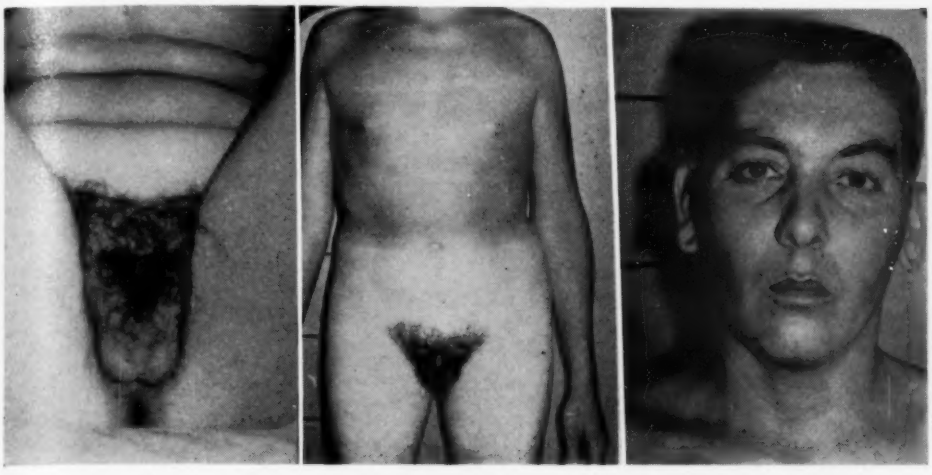

FIG. 7A. S. K., 33-year-old hypogonadal male in whom treatment had been withheld because of anticipation of spontaneous gonadal growth.

FIG. 7B. Patient S. K. Roentgenograms of wrists showing open epiphyses at the distal ends of the ulnae and radii. As anticipated on the basis of these findings, hormonal therapy induced an increase in the size of the genitalia and an increased muscle mass.

might otherwise have been offered an excellent prognosis. Watchful waiting is no more indicated in these young boys than in patients who have a high fever and in whom resolution of the fever is anticipated. Regardless of the possibility of normal though delayed puberty, and regardless of the familial history, initiation of therapy at the time the diagnosis is made should be foremost in the mind of the physician, rather than expose the patient to the dangers of watchful

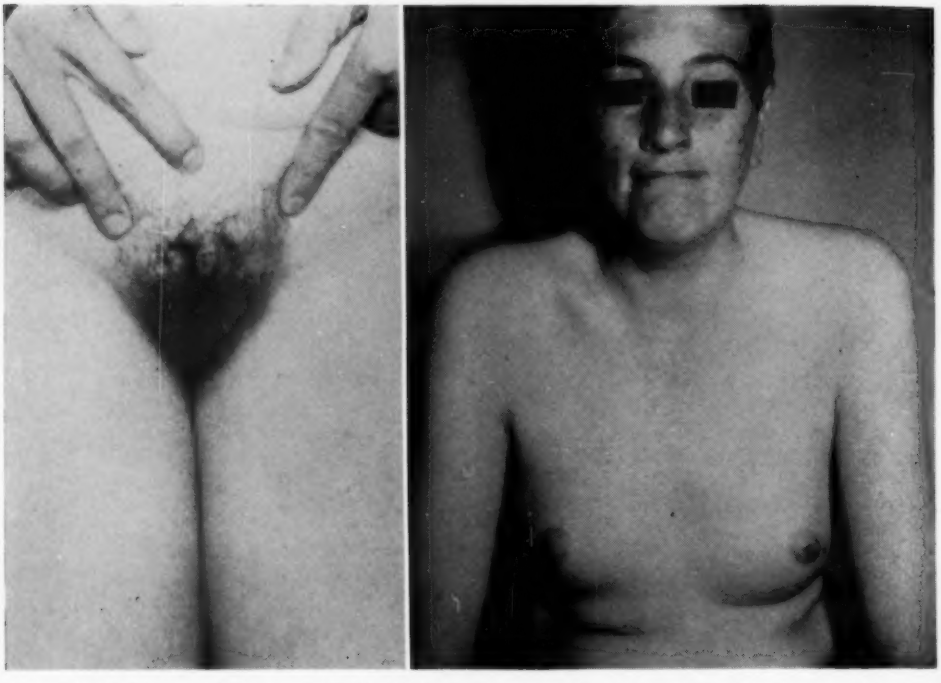

FIG. 8A. S. R., aged 32 years. Tall (72 inches), eunuchoidal male without palpable testes, whose epiphyses were closed. Hormonal therapy (both chorionic gonadotropin and androgens) did not cause any significant change in the size of the penis. Libido was enhanced.

waiting. The end-result for those who watch and wait may be an infantile penis, incapable of functioning adequately as a sexual organ for the male who may be mature in all other respects.

One argument of those who are proponents of the philosophy of watchful waiting is that exogenous hormonal acceleration of gonadal development is unphysiologic and contrary to the laws of nature, which they hold to be irrevocable and not to be tampered with by the skills of men. In addition, they claim that premature epiphyseal closure may occur as a consequence of stimulation by exogenous hormones. They assume that the overall height achieved as a result of hormonal therapy will perhaps be less than the height of a person who has not been subjected to endocrine treatment. In contrast, we feel that acceleration of penile and testicular development by the use of proper hormonal therapy in cases of hypogonadism does not have any adverse effects upon the future height or function of the patient, since treatment in these cases involves the use of gonadotropic hormone rather than steroid hormones. Androgenic steroids *will* cause development of the penis without concomitant increase of testicular size or stimulation of testicular function, and they are contraindicated because their use may promulgate further inhibition of the size of the testes which are already hypoplastic.

When the decision for therapy is made, the following is considered the most effective approach. In patients below the age of 9 or 10 years, 500 I.U. of chorionic gonadotropin (A.P.L.—Ayerst) is administered intramuscularly three times a

FIG. 8B. Patient S. R.. Close-up, showing absence of testes and scrotum

week for three weeks, then twice a week for three weeks; in addition, one of the anabolic steroids, such as norethandrolone, is given orally in a dosage of 10 mg. per day. In patients above the age of 9 or 10 years 1,000 I.U. of chorionic gonadotropin is administered three times a week for three weeks, then twice a week for three weeks, with the dosage of norethandrolone being 10 mg. twice a day for three weeks, followed by 10 mg. daily thereafter. Obviously an "average dose" schedule is fraught with complications, and the clinician must temper such recommendations with the size and body build of the patient and the degree of hypogonadism present. An unusually large 8-year-old child might receive the dosage advised for a 10-year-old boy; an asthenic, small 11-year-old child with mild hypogonadism might respond well to the dose recommended for the boy 9 years old or younger. The patient is evaluated eight weeks after initiation of treatment, and if additional chorionic gonadotropin therapy is indicated, another course may be started a month or two later. A single course is usually sufficient. The younger the patient, the more responsive he will be to the administration of gonadotropic hormone. As a rule, an adequate gonadal effect may be expected following chorionic gonadotropin therapy, if the epiphyses are open. If the patient is in the older age group and the epiphyses are closed, a poor response can be anticipated.

In those patients who fail to respond to chorionic gonadotropin in the recom-

mended dosages, the possibility of testicular failure must be considered. If present, persistent use of chorionic gonadotropin therapy will continue to be ineffective. Lack of response to chorionic gonadotropin is rare, but when it occurs it may be regarded as an indication of unresponsive testes. The prognosis in these patients is poor, and they have to be maintained by replacement therapy with androgenic steroids. Watchful waiting in such cases would never have uncovered the primary defect; consequently, there would have been delay in the use of steroidal therapy, and meanwhile typical eunuchoidal changes would have occurred. Although androgenic therapy does not reverse the infertility, it can stimulate adequate anatomic development so that there will be satisfactory sexual performance in adulthood.

Chorionic gonadotropin in the recommended dosages may also be employed in patients with bilateral or unilateral cryptorchidism, in an attempt to induce descent of the testes. Further discussion of cryptorchidism is beyond the realm of this paper. However, we wish to emphasize that "descent" of the penis is as important a problem as the descent of the testes in patients with small stunted penile structures.

As a result of the described program of therapy, one may anticipate, in addition to the increase in the size of the genitalia, a beginning development of pubic and axillary hair. These are not undesirable side-effects, but are manifestations of the therapeutic response of the patient to the stimulation of production of his own endogenous steroids. Occasionally bilateral gynecomastia, with or without tenderness, may develop after the use of chorionic gonadotropin in the preadolescent hypogonadal male. This is an undesirable side-effect, but it will usually subside when therapy is discontinued. A similar condition often appears and disappears spontaneously during natural pubescence.

CONCLUSIONS

In contradistinction to the watchful-waiting philosophy of the therapeutic nihilist, we believe that in the young male with hypogonadism, early institution of gonadotropic therapy is of prime importance, not only because of the physical disability but because of associated psychologic factors. The physician seeing such patients should be familiar with the use of the gonadotropin and realize that any untoward or undesirable side-effects predicted are more myth than fact. The appropriate dosages and the duration of therapy have been outlined but may also be judged according to the following jingle:

Good, better, best
Never let it rest
Till the good is better
And the better best.

Acknowledgments

Appreciation is expressed to Dr. John Jewell of Ayerst Laboratories for generous supplies of chorionic gonadotropin (A.P.L.), to Dr. Martin Sampson of Smith, Kline and French for the supplies of *l*-triiodothyronine (Cytomel), and to Dr. Robert Craig of G. D. Searle & Co. for making the norethandrolone (Nilevar) available for this study.

TERM GESTATION FOLLOWING TOTAL GASTRECTOMY*

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Gastro-intestinal symptoms occur frequently during the course of any given pregnancy. They may vary from mild "morning sickness" to severe gastro-intestinal hemorrhage or disabling constipation. The physiologically perfect woman is rarely, if ever, seen.

Study of the complications of pregnancy has favorably affected the mortality and morbidity of parturition, and modern therapy in every field of medicine has improved the practice of obstetrics. Surgery has removed obstacles to pregnancy by the effective treatment of pathologic sequelae of disease, congenital abnormalities, or disabling physical injuries. Mitral valvulotomy, segmental pulmonary resection, lumbar sympathectomy, and restoration of tubal patency are only a few examples.

Current therapeutic measures have almost eliminated maternal mortality caused by such disorders as diabetes, tuberculosis or the pernicious vomiting of pregnancy, and they also support the woman handicapped by a solitary kidney or lung, or extirpation of the thyroid gland. At one of our larger clinics in the East, a patient who has had a hypophysectomy is now in her seventh month of gestation. Crohn and his colleagues (1) recently reported their results in a series of 110 women in whom gestation complicated by ulcerative colitis was managed surgically, medically, or by both methods. Davis (2), reporting cases to bear him out, says, "In resecting a portion of the stomach for suspicious ulcer, the general hyperemia of pregnancy might increase operative difficulties but should not prevent the attempt to cure the patient."

Total gastrectomy is rarely undertaken in women, and no references to uninterrupted pregnancy after gastrectomy have been found in the literature. This report concerns the first case in 26,979 deliveries at St. Vincent's Hospital. Gastric lesions are infrequent in the female, and those warranting total resection are rare prior to age 40. They are, therefore, not likely to be observed during a woman's reproductive years.

Physiologically, total extirpation of the stomach (3, 4) presents critical problems of nutrition for both mother and child (5). Removal of this vital organ seriously affects the storage and liquefaction of food, the secretion of hydrochloric acid (6, 7) and the adequate digestion of fat. It also involves the loss of part of the intrinsic factor secreted by the pylorus. Of major importance is the fact that in the absence of hydrochloric acid, the ferric iron cannot be absorbed, and an iron-deficiency anemia may develop.

In this patient, who had had an esophagoduodenostomy, we know that the functions of the duodenum were retained. These functions include the ability to act as a mixing and digesting chamber, and to form important intestinal hor-

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mones such as secretin, pancreozymin and cholecystokinin. Thus, presence of the duodenum affords better absorption of food as well as a diminished tendency towards development of the dumping syndrome after the gastrectomy (4). Because the vagus acts on the intestinal tract by increasing the tonus of the musculature and stimulating glandular secretions of high potency, it is important to preserve the vagal supply. In this case, both the duodenum and the posterior vagal trunk were preserved at the time of gastrectomy.

CASE REPORT

G. W. first presented herself in July, 1956. She was a 41-year-old, white waitress who had been married for sixteen years but had never been pregnant. She weighed 126 pounds and was 5 feet 5½ inches tall. Her father had died at the age of 77 from cancer of the liver, and her mother at the age of 56 from cerebral hemorrhage following a hemorrhoidectomy. The patient had had diphtheria in childhood and a tonsillectomy at age 22.

In 1952, at the age of 36, she had undergone total gastrectomy for an acute spontaneous hemorrhagic gastritis which had not responded to multiple transfusions (a total of 35) before surgical intervention. An esophagoduodenostomy was performed (3), and the postoperative course was reported as uneventful. In 1953 she had a hemorrhoidectomy. Menstrual history had been normal until the time of gastrectomy; after which menstruation was irregular, with a tendency toward amenorrhea every other month. Menstrual flow was scant to moderate, and lasted five days. She had a normal period in January 1956, skipped February, bled in mid-March and again on April 15. She had daily staining from the middle of May to the time of her first prenatal visit. Lower abdominal cramps and pain were present bilaterally and she had two enlarging nodular masses in her lower abdomen. Results of a Friedman test had been positive in early July. She complained of biliousness and dyspepsia, as well as moderate difficulty at defecation, though her two daily stools were formed and soft. Weekly injections of vitamin B_{12} had been continued since the gastrectomy; in addition iron had been administered parenterally every other week.

The patient had had no previous pregnancies and her infertility had been involuntary. Treatment for this primary sterility had been sought ten years before, but had not been successful. In view of her past history, her age, and the presence of fibroids, she had been advised that gynecologic surgery (hysterectomy) was indicated, particularly because it was thought she could not withstand the burden of gestation. However, the patient was most anxious to carry her pregnancy and sought obstetrical care.

Examination revealed an asthenic, though healthy-appearing woman. The head, neck, heart, lungs, and breasts were normal. Blood pressure was 140/78, and pulse rate 78. There was a well healed abdominal scar reaching from the umbilicus to the sternum. The abdomen was not tender, but there was a midline pelvic mass which extended 12 cm. above the pubis and contained knobby protuberances suggestive of fibroids. Pelvic examination revealed a nulliparous introitus with good support and a softened cyanotic cervix which was closed and not eroded. The fundus was anterior, continuous with the abdominal mass, and contained irregular intramural and subserous fibroids. Rectal examination showed skin tabs, and the results of palpation by this route confirmed the pelvic findings.

The diagnosis was normal intrauterine pregnancy with fibromyomata. The expected date of confinement was January 22, 1957.

Laboratory data: Urine normal; hemoglobin level 12.8 Gm. per 100 ml.; red blood cell count 4.3 million per cu. mm.; and serum protein concentration 6.0 Gm. per 100 ml. The Kahn reaction was negative. The blood was type O, RH-positive.

In view of the previous sterility, the patient's age, the fibroids and the past history, it was decided that delivery should be at term by cesarean section, followed by hysterectomy if any evidence of dystocia developed. Clinical evaluation of the pelvis showed a normal gynecoid structure adequate in all its planes for the passage of an average sized fetus.

The patient was seen twelve times during her practically uneventful prenatal course (Table 1). At no time did the blood pressure rise above 132/84; results of all urinalyses were negative; and the weight increased from 126 to 137½ pounds at term.

TABLE 1

Clinical and Laboratory Data in Patient G. W.

	Weight (lbs.)	B.P. (mm. Hg)	Urine Alb.-Sugar	Blood		Ht. of Fundus (cm.)
				Hgb. (Gm./100 ml.)	RBC (million/ cu. mm.)	
Ante partum						
1956						
July 25	126	140/78	0	12.8	4.3	11
Aug. 27	129	130/80	—	13.0	4.6	16
Sept. 29	132½	120/60	0	12.6	4.3	17.5
Oct. 15	134	132/74	0	12.8	4.5	21.5
Nov. 5	136	124/76	0	—	—	20.5
Dec. 3	133½	124/74	—	13.2	4.6	22.5
1957						
Jan. 4	136	120/78	0	12	4.3	24
Jan. 28	137½	128/84	0	—	—	26
Delivery*						
Jan. 31 (Normal female infant weighing 5 lbs. 10 oz.)			0	10.7		
Post partum						
Feb. 2 (Hosp.)	—	114/70	0	10.5	3.6	—
Feb. 8 (Hosp.)	125	118/70	—	—	—	12
Feb. 25	122	120/72	—	10.8	3.8	10
Apr. 10	125	134/78	—	11.8	4.1	6

* Transfusion of 500 cc. of O RH-positive blood.

Supportive treatment included weekly parenteral injections of 25 to 50 micrograms of vitamin B_{12}, 1 cc. of liver concentrate, and 2 cc. of iron-dextran complex (8, 9). She tolerated standard amounts of prenatal mineral and vitamin preparations orally, and responded to daily doses (40–60 mg.) of oral progesterone given for periodic bouts of annoying "menstrual-like" cramps. However, she could not tolerate preparations of ferrous sulfate or molybdate. Prenatally, the only noteworthy complications were an increase in dyspepsia and regurgitation, a two-week illness because of an upper respiratory infection, and occasional bouts of diarrhea. The gastro-intestinal disturbances responded well to the sedative-antispasmodic drugs and strict control of the fat content of the diet.

Labor began spontaneously on January 31, 1957. The patient entered the hospital at 8:30 p.m. complaining of irregular labor pains and some vaginal bleeding. X-ray pelvimetry on admission confirmed the clinical impression of adequate pelvic size and no cephalopelvic disproportion. The cervix was well effaced, dilated 5 cm., and the vertex was low. Pelvic delivery was decided upon. Preparatory medication was given. Labor progressed normally, the membranes were artificially ruptured, and at midnight a normal 5-pound 10-ounce female child was delivered by low forceps. Occult prolapse of the cord caused some transient fetal distress, but the infant responded at once to resuscitative measures. Placenta and membranes were normal, both grossly and microscopically. The mother withstood labor well, but a 500-cc. transfusion of blood was given for prophylactic purposes. Despite transfusion, the hemoglobin level was 10.7 Gm. per 100 ml. the day after delivery. The weight of the patient on the eighth postpartum day was 125 pounds and the concentration of hemoglobin was 10.5 Gm. per 100 ml. The antepartum and postpartum laboratory data are listed in Table 1.

Blood studies on the infant at birth showed a hemoglobin level of 19.8 Gm. per 100 ml., a red blood cell count of 6.5 million per cu. mm. with polychromasia of the erythrocytes, and 1 normoblast per 100 leukocytes. Serum protein concentration was 6.1 Gm. per 100 ml. On discharge, the baby had gained 4¼ ounces with formula feedings.

Twelve weeks post partum the patient had no complaints. Her weight was 125 pounds, blood pressure 134/78 and hemoglobin level 11.8 Gm. per 100 ml. The uterus was well involuted, the fibroids were slightly tender and the stools were normal. The baby had almost doubled its birth weight and weighed 10 pounds 2 ounces.

It is difficult to describe the controlled elation and happiness of this patient at the end of her successful pregnancy. There was no evidence of injury or undue physiologic stress. Three months following delivery she had apparently returned to the pre-gestational alimentary state; her weight was 125 pounds, hemoglobin level 12.0 Gm. per 100 ml., red blood cell count 4.4 million per cu. mm., and serum protein level 5.7 Gm. per 100 ml.

DISCUSSION

This case is presented so that it may be added to reports in the literature of gestation with complications arising from pathologic conditions (10) in the gastro-intestinal tract. It is realized that many patients after gastrectomy are alimentary cripples, and generally fare poorly. They would undoubtedly be very bad obstetrical risks—if they could even become pregnant. However, the patient in this report demonstrates that when adequate nutrition (5) and metabolism have been established after gastrectomy, even the physiologic burden of pregnancy may be borne without undue stress on the mother.

SUMMARY

Pregnancy may occur and be carried to successful termination following total gastrectomy, in spite of the problems of nutrition and metabolism which may influence the status of mother and infant.

A case is presented of a 41-year-old woman who first became pregnant four and a half years after esophagoduodenostomy for benign disease. At term, a healthy infant was delivered normally, despite the complications of the mother's age, primiparous state, long prior sterility, and the presence of large fibromyomata of the uterus.

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THE ROLE OF THERAPEUTICS IN MEDICAL EDUCATION*

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Consistent with the continuous and periodic variations, changes and advances in medicine, treatment as such finds itself in ever-changing relationship in the pattern of practice and in the curriculum of medical education. To appraise the role of treatment today in the education of the physician, we must recognize its position in the recent past and the trend in the future. Around 1900 we were living through a period of few specific drugs, a tendency toward therapeutic nihilism, and feeble and only partially effective symptomatic treatment. By the 1920's the profession at large, perhaps more than the educators, was becoming concerned that so little instruction in therapeutics was being given in the medical schools. The faculties were being criticized because the medical student was being taught poorly in the art and skill of prescription-writing. Courses and departments of therapeutics and materia medica were disappearing, and the scope and contents of these courses were being absorbed into other courses, thereby losing the identity of therapeutics as a separate and distinct segment in the educational process. These same criticisms may seem valid today in a superficial look at our educational pattern. On the other hand, a more profound survey reveals that instruction in treatment as it pertains to the total study and care of the patient has not diminished; indeed it has increased, through integration with the instruction in several departments of the medical schools, hospitals, and other health agencies as they exist today. In this integrated form of medical education, the treatment of disease occupies more time and attention than it has at any time in this generation of physicians, and rightly so, in view of the recent advances in the knowledge and availability of so many effective therapeutic agents and methods.

The ultimate goals of the physician in the care of the patient are to prevent illness, to cure or eradicate disease when it occurs, to relieve untoward symptoms, and to aid in the return to health. The therapeutic agents, methods and techniques by which the physician attains these goals are many and comprehensive; they involve every field and specialty in medicine. Treatment occupies a most important place in the whole educational scheme, not only at the undergraduate but at the graduate and postgraduate levels. The big problem is the manner, the place, and the implementation of the teaching of therapeutics in the already extensive and complicated medical curricula. There is a slow-boiling and continual restlessness among medical educators, and much discussion and deliberation among curricular and educational committees regarding how best to improve the methods of presenting this type of instruction and training to the students and the profession in a form which is both stimulating and progressive.

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It is recognized that the diagnosis of the disease or physiologic disorder, and the origin and nature of the symptom complex must be established in order to apply treatment properly. The selection of available therapeutic agents and measures and their effective administration is dependent on the knowledge, skill and ability of the physician. In some instances the proper therapy (which is often known by present-day patients) is so comprehensive and complicated as to require not only a team of physicians and allied personnel but even special facilities and equipment for its administration. It becomes the function and responsibility of the medical educational process to train the medical student in these disciplines, inspire in him a desire for further knowledge, and even to project for him the methods and techniques of continued self-education after he has departed from medical school and other sources of formal instruction and training.

TRENDS IN MEDICAL EDUCATION

Let us explore some of the trends in medical education. Treatment in all of its types and phases is an inherent component and eventually is the practical application in any educational pattern in the training of the physician.

Pre-professional and medical school education takes seven or eight years at present. It is impractical and inadvisable to extend this period. There is current consideration of schemes to hold this situation in check, and to shorten the period of medical education by combining the pre-professional with the basic professional years. This idea is not new, but it still involves many problems. There is an ever-increasing tendency to extend internship-residency programs, both in the field of general practice and in the specialties. Sooner or later circumstance limits this expansion, and socio-economic factors play no small part in the application of these advances.

In the area of the undergraduate medical school there is a growing tendency to coordinate and integrate the teaching of basic sciences with the teaching of clinical subjects, to introduce these students earlier to clinical subjects, to decrease the number and content of didactic lectures, to increase the number and scope of conferences in small seminars and other forms of discussion exercises, and to increase the use of clinical clerkships for teaching purposes. These innovations allow the students more time with the individual teacher, the patient, the library and the laboratory. The student travels with the teacher as a colleague, associate and assistant. He learns to do, by doing. In effect this is the 1957 model of the preceptorship type of training and education. These trends have been considered good, progressive, and the most effective method up to now for gaining and applying the vast amount of knowledge required in preparation for the practice of medicine. The internship and residency programs are extensions of this philosophy of medical education. Therapeutics is included inherently and realistically, and often without formal or specific identity, in this educational scheme.

EDUCATIONAL MEDIA

There is an ever-growing mass of educational media. Numerous current medical periodicals for the general practitioner and the specialist present current

reports on materials and methods, so that the information does not become obsolete or out-moded. Textbooks are now much more up-to-date at the time of their publication than formerly. County, state and national medical societies in their scientific meetings bring new developments closer to the profession. A myriad of postgraduate courses of many types are more easily available for the physician today. Therapeutics comes in for its proper share of attention in all of these educational endeavors. The great problem in medical education is to discern in what way the physician can become all-knowing, or at least conversant with all the new information, so that he can apply it to the benefit of the patient. Because of the nature of the practice of medicine, there is hardly enough time for the physician to consult a great number of sources for this information; much of it must be brought to him in some fashion, and he must have established an effective method of continual self-education. The current medical literature probably will be the most effective agent, aside from a limited attendance at medical meetings and postgraduate courses. Participation of the physician in the educational activities of local hospitals and other health agencies broadens the opportunities for self-education. Many of the articles in current medical journals and papers are written by the participants in local meetings and conferences, and they deal predominantly with the matter of treatment.

Nevertheless, there is need for easily available source material in therapeutics for the convenience of physicians in every-day practice, whether general or special. The general practitioner needs to be conversant with the therapeutic materials and methods of the specialist, and it is obvious that the specialist at times needs the benefit of knowledge of therapeutics outside his own limited field. It is particularly difficult and probably only partially possible to compose an educational package of this kind. In the organization of the knowledge and application of treatment within the comprehensive integrated medical educational pattern of today, it seems necessary to divide such a packaged educational medium into several categories. These categories include: 1) specific drugs or methods of treatment for specific diseases, 2) symptomatic treatment to ameliorate the symptoms which accompany the disease or physiologic disorder, or which remain after the use of the specific agent, 3) classification and listing of therapeutic agents, with guidance as to selection, methods of administration, therapeutic action and toxic reactions, 4) and special therapeutic procedures, methods and techniques. It is a real challenge to medical education to implement the teaching of therapeutics in training of the physician.

In closing, it would seem most appropriate to recall the words of Francis Weld Peabody:

"The good physician knows his own patients through and through, and his knowledge is bought dearly. Time, sympathy, and understanding must be lavishly dispensed, but the reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in the caring for the patient."

THROMBOANGIITIS OBLITERANS: A 30-YEAR STUDY*

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Thromboangiitis obliterans was established as a disease entity by the results of the clinical and pathologic investigations of juvenile or presenile gangrene reported by Buerger from 1908 to 1924 (1). The roles of infection, allergy and endocrine disturbance in the etiology of the disease have been studied intensively for the past fifty years; however, they still are not accepted as causative factors. Recent advances in our knowledge of the pathologic anatomy and the experimental production of atherosclerosis and repair have revived the earlier concept of the disease on the basis of presenile arteriosclerosis (2). This report is presented with the view to interpreting the pathologic findings in thromboangiitis obliterans in the light of our present knowledge of atherosclerosis, and to discuss treatment.

CLINICAL AND PATHOLOGIC OBSERVATIONS

Among more than 4,000 patients who were examined for peripheral arterial disease in the past thirty years, there were 139 young adults with organic arterial occlusion which was diagnosed as thromboangiitis obliterans. In 2 of the patients there was a serologically positive reaction for syphilis, but there was no history or other evidence of the infection. The clinical and pathologic observations on these 139 cases of thromboangiitis obliterans were studied for the following information: 1) the clinical course of the disease in the past thirty years; 2) the pathologic findings in amputated extremities and in autopsy cases; 3) roentgenographic (arteriogram) abnormalities of arteries and arterioles, both *in vivo* and in amputated extremities; and 4) the effectiveness of treatment.

The clinical course of the disease has changed greatly since we studied and treated our first cases in 1927. At that time there were no effective methods for relieving the symptoms or altering the progressive course of the disease. As recently as 1938, Craig and Horton (3) reported that 42 per cent of the patients with thromboangiitis obliterans at the Mayo Clinic had had amputations; 68 per cent of these were major amputations. During the past twenty-five years, a definite program for the management of these cases has been evolved and has been effective in relieving the acute symptoms, in improving the peripheral circulation, in controlling infection, and in healing areas of necrosis and the wounds of local amputation. There have been no major amputations for thromboangiitis obliterans in our hospital for sixteen years.

In the early years of our study, extremities amputated for necrosis, gangrene, infection and pain, provided the material for pathologic investigation of the peripheral arterial lesion. The gross and microscopic findings described and

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illustrated by Buerger were confirmed by us. The characteristic arterial lesion is that of arteritis with segmental occlusive thrombosis and perivasculitis. Different stages of the obstructing thrombus may be present—from the older organized fibrous cord attached to the vessel to the more recent propagating conical unattached clot where the artery is normal. There is histologic evidence of atheroma in the arterial lesion. The typical vasculitis, perivasculitis, and thrombosis occur only in the lower extremities below the knees as pointed out by Buerger. At this location, the venae comites with lymphatic channels completely surround the arteries. Although slight calcification may be present in the arteries of amputated extremities, specimens obtained at re-amputation after an intervening period of years, may exhibit marked arteriosclerosis.

Autopsy material is usually obtained years after the onset of symptoms or after extremities have been amputated. The usual long nonfatal course of the peripheral disease, with periods of remission and recurrence, has made autopsy studies scarce. Buerger reported only 3 autopsies in his vast clinical material, and we have had only 4. In his 3 autopsy cases there was extreme atherosclerosis and thrombosis of the abdominal aorta in patients 21, 24, and 35 years of age, respectively. In our 4 autopsies there were similar findings. One specimen, from a woman 29 years of age who had suffered from the disease for ten years, showed complete fibrous-tissue occlusion of the terminal aorta and atherosclerosis and thrombosis of the proximal aorta. Another specimen, from a man 49 years of age who had had the disease for twenty-five years and had lost toes from both feet, demonstrated profound atherosclerosis and arteriosclerosis of the entire aorta with almost complete thrombotic occlusion of the terminal aorta (Fig. 1, a and b). Another specimen, from a man 40 years of age who had undergone amputation of one leg, showed advanced atherosclerosis and arteriosclerosis of the entire aorta with thrombosis that extended into the mesenteric artery. Other arteries were also involved in the atherosclerotic process.

At the time of Buerger's investigations, little was known about the atherosclerotic and arteriosclerotic lesions that were found regularly in his pathologic specimens. He noted, however, that "marked atherosclerosis is not uncommon in relatively young individuals in whom thromboangiitis obliterans is never a complication." He considered these findings as "associated arteriosclerosis," but our recent knowledge of the origin of thrombosis at the site of an intramural hemorrhage or rupture of an atheromatous plaque accounts for his misinterpretation of what is probably merely an associated factor in the disease. Until Cowdry's publication (4) on arteriosclerosis in 1933, there had been no effort to concentrate our knowledge on the subject. In 1935, Leary (5) described atherosclerosis as the important primary stage of arteriosclerosis. To consolidate present knowledge and to stimulate further investigations, the Air Force Directorate of Research and Development published the papers presented at the Symposium on Atherosclerosis (6) in 1954. Some of the reports on the reparative tissue reaction to atheromata are significant in explaining pathologic vascular findings in thromboangiitis obliterans, except for the failure to produce thrombosis experimentally.

Atherosclerosis is accepted as a metabolic disease with important lipid relation-

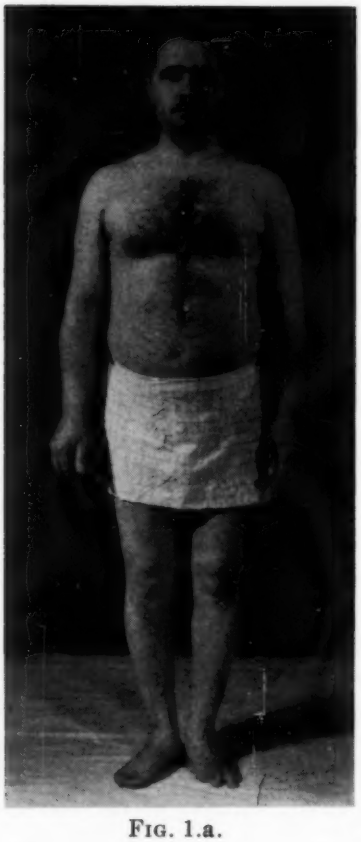

FIG. 1.a.

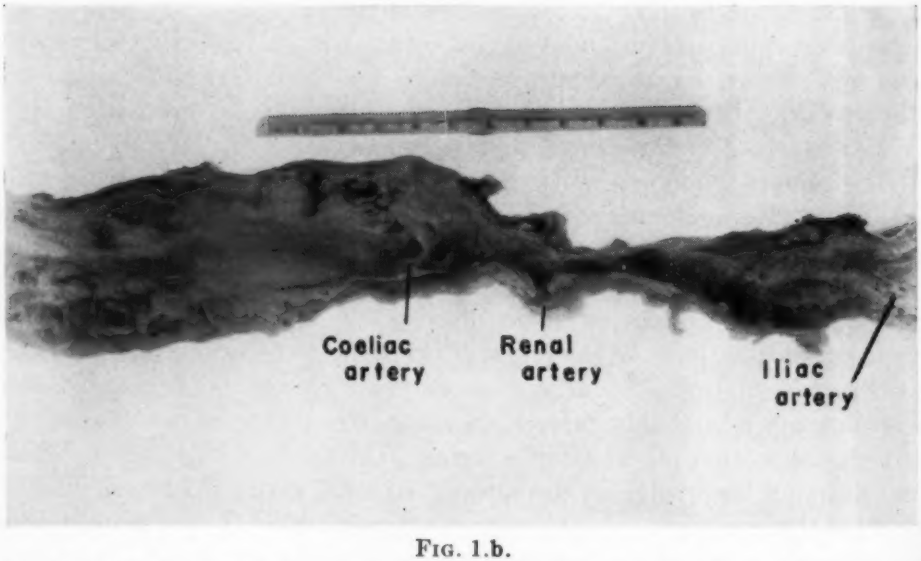

FIG. 1.b.

FIG. 1. **a**. Patient with advanced peripheral arterial occlusion due to thromboangiitis obliterans. Loss of toes of both feet occurred at the age of 33 years. Following treatment, marked clinical improvement permitted him to return to his previous occupation as a barber. Death occurred at the age of 49 years due to coronary occlusion. There had been no recurrence of peripheral necrosis or gangrene in the extremities.

b. Advanced atherosclerosis and arteriosclerosis of the entire aorta with thrombosis of the terminal aorta and both common iliac arteries.

FIG. 2. Cross-section of popliteal artery from a 34-year-old patient with thromboangiitis obliterans, showing an extremely large arteriosclerotic plaque, the base of which has a foamy-hyaline appearance (A), suggesting the presence of lipid material. Focal calcification is present in the plaque (B), and in the media and internal elastic membrane.

ships (7). The occurrence of atherosclerosis in young persons (Fig. 2) is relatively common, but the sequence of events leading to partial or complete occluding intravascular thrombosis and to the vascular inflammatory and reparative tissue reaction have been described only recently. Winternitz (8), Hass (9), Paterson (10), and others have noted that hemorrhage from newly formed capillaries in atheromata may produce serious acute swelling of the atheroma or, as more frequently occurs, superficial necrosis and thrombosis leading to occlusion of the arterial lumen. Organization of each new hemorrhage or small mural thrombus leads to further fibroblastic growth, new capillaries, and recurrent hemorrhage and mural thrombi. Blood pigment, hemosiderin, and giant cells are found in many of the typical vascular lesions of thromboangiitis obliterans. The occluding or partially occluding thrombi become progressively enlarged by recurrent deposit and finally become organized into a dense mass of collagenous tissue. The end-result, as one might expect in thromboangiitis obliterans, is an organized fibrous mass which permanently stenoses the arterial lumen (Fig. 3). Some of the vascular and perivascular inflammatory reaction could be due to the close anatomic arrangement of the venae comites and lymphatic channels, especially

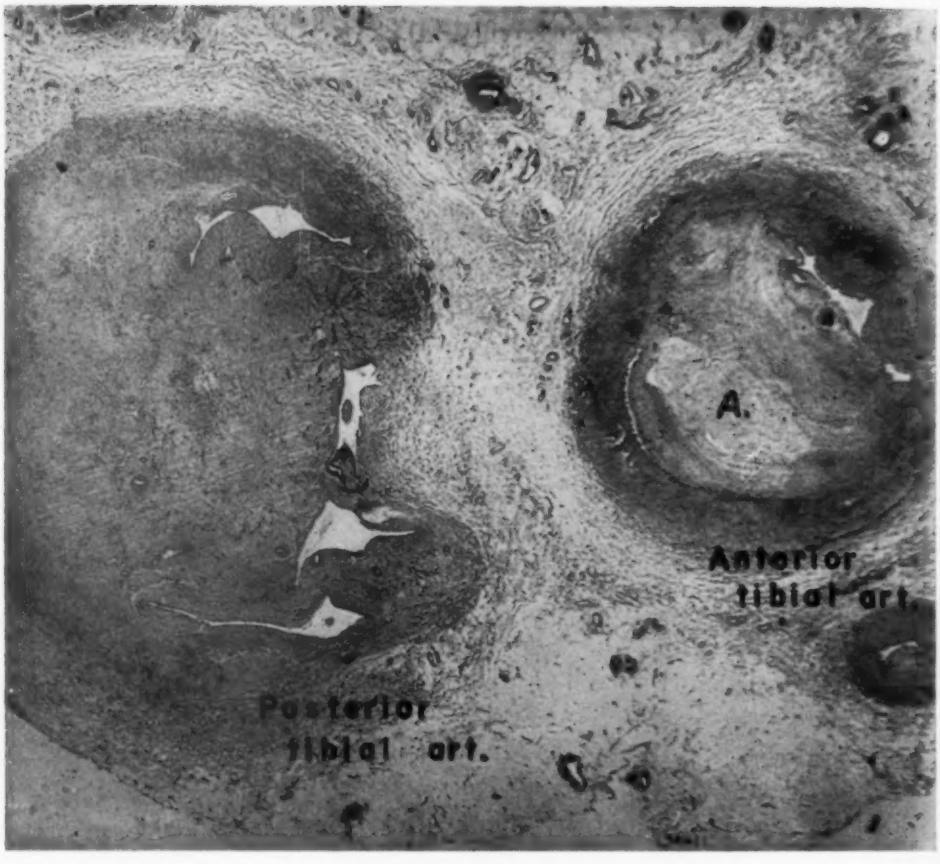

FIG. 3. Cross-sections of anterior and posterior tibial arteries in thromboangiitis obliterans (patient aged 44), showing organization and recanalization of thrombus. There are four larger, and numerous smaller recanalized channels. The stroma is made up of dense connective tissue which extends to the extreme margin of the vessel. The smaller artery exhibits extremely severe arteriosclerosis involving a huge plaque and an eccentric, slit-like lumen which is greatly narrowed. The plaque has a foamy-hyaline appearance (A), suggesting the presence of lipid.

important when necrosis, gangrene and infection are present in the extremity. It is known that characteristic giant cells are observed when cholesterol and cholesterol esters occur in crystalline form. There may be differences in atheromatous lesions, for Waters (11) has reported that fat tends to disappear from atheromata in young and emaciated persons.

Roentgenologic studies were made of the vascular tree in cases of thromboangiitis obliterans, both *in vivo* and in amputated extremities. In the latter, radio-opaque material was injected into the popliteal artery, and the arteriograms showed segmental arterial occlusion and well developed collateral circulatory channels (12), which were in striking contrast to the complete and extensive arterial occlusion and poor collateral channels found in limbs from elderly people with advanced artherosclerosis and arteriosclerosis. In the patients themselves, plain x-ray film exposure of the aorta or peripheral vessels did not

show any calcium deposits. In 16 clinical cases, arteriograms revealed irregular narrowing of the lumen of the aorta, iliac or femoral arteries and areas of segmental occlusion. In a 17-year-old youth with clinical evidence of peripheral arterial occlusion, arteriograms showed irregular narrowing of the entire femoral artery and a segmental area of complete occlusion. Arteriograms are invaluable in demonstrating disease of the proximal arteries and dilated collateral circulatory channels to account for the frequent absence of serious circulatory deficiency and gangrene (Fig. 4, a, b and c).

TREATMENT

Our program of treatment has met with encouraging results. Symptoms have been relieved and objective clinical improvement has been demonstrated. While the patients have been under our observation there has been little, if any, advance of the disease in the involved extremity or extension to other extremities. Patients have been ambulatory, except for periods of hospitalization required for surgical treatment. Characteristically they have remained unusually sensitive to cold. Recurrent or migrating thrombophlebitis developed in 4 cases, but was associated with trauma or an attack of acute respiratory infection, tonsillitis or pharyngitis. During the past sixteen years there have been no major amputations in our group of cases, and areas of gangrene have been removed only after local infection was controlled and a line of demarcation had formed.

On the assumption that thromboangiitis obliterans is a manifestation of juvenile atherosclerosis obliterans, treatment is directed toward: 1) improving or correcting the serologic and metabolic changes that contribute to the vascular disease and to the thrombosis, 2) increasing the collateral circulation in the involved extremities, and 3) controlling infection in the toes or foot. Successful treatment depends upon effective measures for each of the foregoing factors.

Altered morphologic and chemical constituents of the blood which may contribute to occlusive vascular disease have received widespread attention. Since thrombus formation is the cause of arterial obstruction in thromboangiitis obliterans, treatment should be directed toward decreasing the clotting tendency of the blood. Although the appearance and consistency of the blood in the active stage of thromboangiitis obliterans is grossly abnormal, the results of blood studies have been neither uniform nor verified. This may be due to our present inability to detect clinically the early stage of the disease. Increased viscosity of the blood was reported by Koga (13) in 1913; however, there still is no accurate method of measuring blood viscosity. Silbert (14) and Samuels (15) recommended intravenous hypertonic salt solution to decrease the viscosity of the blood. Steele (16) used sodium citrate solution to reduce the clotting activity, and Rabinovitz (17) advised sodium iodide thiosulfate because of its chemical effect on lipoproteins. Anticoagulants and many other drugs have been advocated as effective in correcting the various blood changes.

In 15 cases, we found low oxygenation of the arterial blood (18) during the active or acute stage of the disease; there was a return to normal associated with the clinical improvement that followed treatment with sodium thiosulfate or

FIG. 4.a

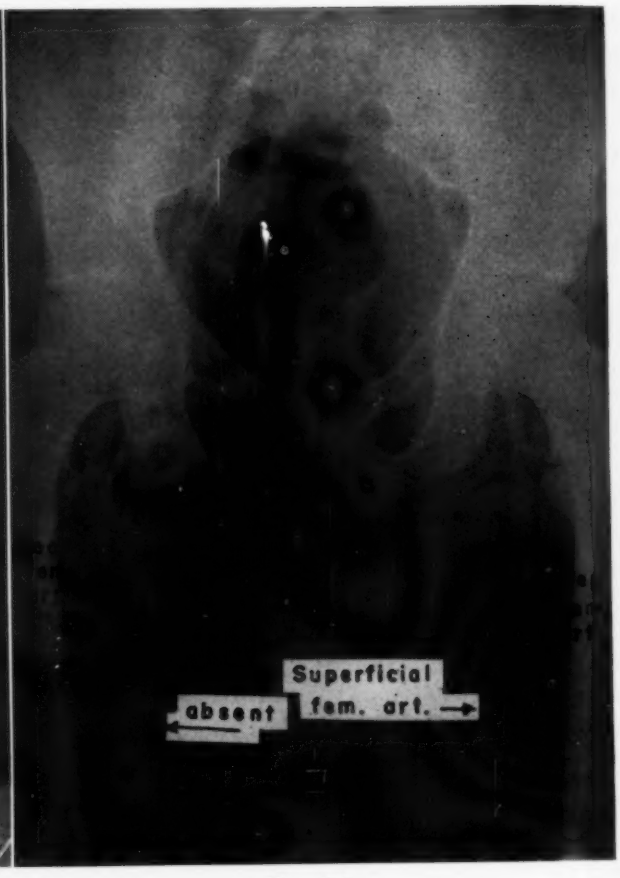

FIG. 4.b.

FIG. 4.c.

TABLE 1

Changes in Oxygen Saturation and Cholesterol Level of the Blood Following Treatment in a Case of Thromboangiitis Obliterans

Mr. E., aged 32. Initially the oxygen saturation of the arterial blood was low, but it returned to normal following intravenous injection of sodium tetrathionate. With clinical recovery, the serum total cholesterol concentration reached high-normal levels.

	O_2 Cap. (vol. %)	O_2 Sat'n (%)	Total Serum Chol. (mg./100 cc.)
March 1, 1949			
Before inj. of sodium tetrathionate	17.3	65.4	209
After inj. of sodium tetrathionate	17.3	86.5	—
April 4, 1949			
After 18 injections of sodium tetrathionate	18.1	93.8	—
May 19, 1949			
After sympathectomy (right leg)	16.8	80.6	161
June 21, 1949	17.5	93.0	150
Feb. 11, 1953	18.2	94.4	259
Jan. 13, 1956	18.0	97.0	219

sodium tetrathionate. Table 1 shows the results in a representative case. Whatever the final interpretation of the action of these drugs may be, our observations have led us to believe that they are of unquestionable benefit. Anfinsen's (19) recent investigations have shown that certain sulfate-containing drugs act in a similar way to heparin on the serum lipoproteins. In many patients, during the active stage of the disease, the clotting and prothrombin times are rapid, and this may explain the unusual intravascular clotting in thromboangiitis obliterans. In 4 acute cases the prothrombin concentrations (by the two-stage method) ranged from 120 to 130 per cent.

Atherosclerosis is linked experimentally and clinically to abnormal lipid and cholesterol metabolism, usually associated with elevated serum lipid and cholesterol levels. However, in thromboangiitis obliterans the concentration of serum cholesterol is, with rare exceptions, within normal limits and usually under 200 mg. per 100 cc. Investigations on lipid metabolism, reported in the Symposium on Atherosclerosis, may provide an explanation for the development of early atherosclerosis in the presence of a low serum cholesterol level; the same factor(s) may contribute to the unusual tendency toward intravascular clotting in thromboangiitis obliterans. After clinical recovery, these patients tend to become obese. The concentration of serum cholesterol varies, and may rise as high as 350 mg. per 100 cc. This effect is largely dietary and is controlled readily by a low-fat, low-cholesterol, low-calorie diet. The basal metabolic rate (20) may

FIG. 4. a. Patient, aged 32 years, with advanced thromboangiitis obliterans due to occlusion of the peripheral arteries of the right lower extremity.

b. Arteriogram showing occlusion of the superficial femoral artery and minimum collateral channels.

c. Infected gangrene of right fourth toe. Limited gangrene of the toe resulted from severe circulatory deficiency of the entire extremity.

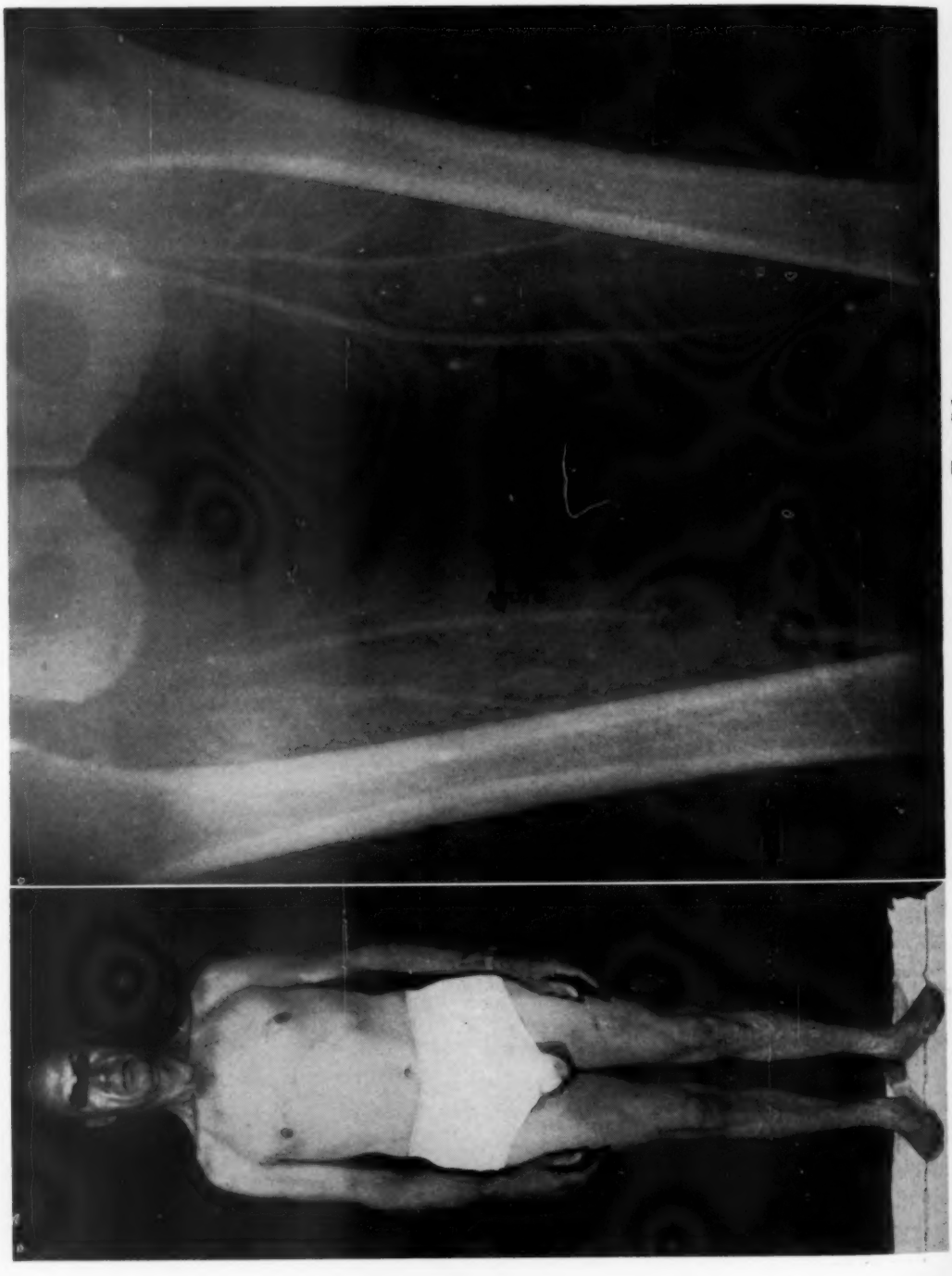

FIG. 5.b.

FIG. 5.a

be as low as −20 to −30 per cent associated with a low pulse rate; in these instances thyroid medication is prescribed to elevate the pulse rate to 70 or 80, and to raise the metabolic rate toward normal.

Peripheral circulatory deficiency resulting from the segmental arterial occlusion is accompanied by a variable degree of collateral vasoconstriction. It is recognized that smoking increases the vasoconstriction (21) and the peripheral circulatory deficiency, and that it should be discontinued permanently.

Irrespective of the degree of vasospasm demonstrated by diagnostic tests, lumbar sympathectomy has proved to be of value in improving the collateral circulation and in eliminating hydrosis in the extremities. The progressive course of the systemic disease, however, remains uneffected by this operation (Fig. 5, a and b).

Infection of the toes or feet is usually secondary to trauma of the skin. Proper hygienic care and strict surgical asepsis are necessary in all cases when there is deficient circulation. Previously, poor circulation was assumed to account for most cases of gangrene and for the difficulty in controlling infection. Routine cultures from open wounds frequently demonstrate symbiosis of infective organisms such as the staphylococcus, streptococcus, pseudomonas, aerobacter aerogenes and others. In some instances, the results of sensitivity tests indicate the presence of organisms that are resistant to all available antibiotic and chemotherapeutic agents. Pseudomonas and the aerobacter aerogenes organisms are the most resistant to treatment. When the infection is treated with properly selected antibiotic agents, wound healing ensues with minimum loss of tissue.

SUMMARY

During the past thirty years, more than 4,000 patients were examined for peripheral arterial disease; in 139 young adults with organic arterial occlusion the diagnosis was thromboangiitis obliterans. The clinical course of the disease has improved greatly since our first cases were studied and treated in 1927. No major amputation has been necessary for the past sixteen years. In patients under our observation for periods of eight to twenty-four years, there has been no advance of the disease to involve other limbs to any significant degree.

Study of amputated extremities and autopsy material has demonstrated that thromboangiitis obliterans is a progressive generalized arterial disease. It initially appears in the extremities as segmental arteritis and occlusive thrombosis, and is related to atherosclerosis. Only recently, this thrombosis has been shown to be due to intramural hemorrhage and ulceration of an atheromatous plaque. Arteriograms of the arterial tree *in vivo* and in amputated extremities

FIG. 5. **a**. Patient with advanced bilateral arterial occlusion due to thromboangiitis obliterans. There was serious disability as a result of peripheral circulatory deficiency but no gangrene or infection. Excellent clinical improvement followed right and then left lumbar sympathectomy.

b. Arteriogram showing extensive irregular narrowing of the arteries of both lower extremities and complete occlusion of the lower right femoral artery. Three months after right lumbar sympathectomy, a complete occlusion of the left femoral artery required lumbar sympathectomy.

demonstrate extensive proximal involvement of the arteries, areas of segmental occlusion, and dilated collateral vascular channels.

Results of blood studies are equivocal. However there are definite alterations in the blood, and these may be important in interpreting the early development of extensive atherosclerosis in the absence of hypercholesterolemia and of occlusive thrombosis. Increased blood viscosity, increased hemoconcentration, rapid clotting, abnormal serum lipoprotein content, and low oxygenation of the arterial blood (as reported in the literature) may contribute to the clinical and pathologic course of the disease. Almost all deaths have been due to advanced atherosclerosis with occlusive thrombosis in vital organs.

Successful treatment depends upon effectiveness in: 1) improving or correcting the morphologic and chemical (lipid) alterations in the blood and other tissues that may contribute to the arterial disease and to the occlusive thrombosis, 2) increasing the peripheral collateral circulation, and 3) controlling infection in the involved extremity.

CONCLUSIONS

A process of atherosclerosis, occlusive thrombosis and reparative reaction seems to account for the peripheral arterial lesions of thromboangiitis obliterans or presenile gangrene.

Reported changes in the blood may be a factor in the generalized atherosclerotic process in the absence of hypercholesterolemia, the occlusive thrombosis in the extremities, and the unusual reparative tissue reaction in the peripheral vascular lesions.

Treatment directed toward correcting the blood abnormalities, the peripheral circulatory deficiency, and infection in the toes or feet, has been successful in ameliorating the active stage of the disease and in improving the long-term prognosis.

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THE USE OF PLASMIN IN THE TREATMENT OF INTRAVASCULAR THROMBOSES*†

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The use of enzymes as therapeutic agents is not entirely new. John Hunter used a crude pancreatic extract for debridement of wounds, and it is probable that maggot therapy was successful because of enzymes produced by the maggots. Trypsin, papain and streptokinase-streptodornase (Varidase) have been used extensively (1). Except perhaps in the case of trypsin, these were crude, cumbersome and sluggish methods of treatment. Today, we are standing on the threshold of truly significant advances in this field. Many more purified and more potent enzymes are being produced, and our understanding of their activities, functions and inhibiting substances is growing daily.

One of these new enzymes is plasmin (fibrinolysin), which has been studied as a therapeutic agent for three to four years (2–3), Plasmin is present as an inactive precursor (plasminogen) in the plasma of most, and perhaps all animals. It is activated by tissue, blood and urinary activators and by organic solvents such as chloroform, among others. The best activator for human plasminogen is streptokinase (SK) which acts in one of two ways: 1) on a pro-activator in plasma to produce an activator which then acts on the pro-enzyme itself to produce the active proteolytic and fibrinolytic enzyme plasmin, or 2) on the pro-enzyme to produce plasmin, to which additional units of SK are attached to produce an activator. We favor the first explanation.

Inhibitors of SK and of plasmin are present in the blood of all persons, but under certain circumstances the inhibitor unit becomes very high. This is especially true of SK inhibitors after streptococcal infection—the foundation for the anti-streptokinase test for streptococcal infection (4). Methods of testing the enzymes and blood for activity and methods of testing for inhibitors are available, but need to be improved.

Plasmin was first used in animals to lyse intravascular clots and was found to be very effective (5–6). In human subjects, rather than risk toxic reactions from intravenous use, we decided to try it first in local conditions. As previously reported, we observed only rare and minimal reactions even with prolonged local use. In chronic ulcers, especially varicose ulcers, debridement is rapid and healing improved (7). Even in arteriosclerotic ulcers of the feet and heels in the aged, healing can be expected with prolonged use in 75 per cent of cases.

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Chronic wound infections, sinus tracts and abscess cavities were next treated. Fifty cases were reported in two previously published papers (8–9). Since that time over 50 additional patients have been treated with equally good results. Rapid debridement was almost universal and healing occurred in over 90 per cent of the cases with continued treatment. No significant, local or general reactions were observed, even with prolonged use. Some cases of old chronic osteomyelitis or foreign bodies were treated for as long as three months without reactions.

USE OF PLASMIN FOR INFECTED WOUNDS

More recently we set up at Bellevue Hospital a program to study the effect of plasmin on acute abscesses after incision and drainage. The cases were divided into 3 groups. One group was treated with antibiotics plus standard dressings, a second with plasmin plus antibiotics, and the third with plasmin alone. Biopsy specimens from the abscess wall were taken daily for culture. The abscess cavities treated with plasmin became clean and practically sterile in about half the time required for those treated with the usual dressings and antibiotics; in the plasmin-treated wounds, dressings were necessary only once a day as compared with two to four times daily under the other regimen. Subsequently, plasmin-antibiotic therapy was abandoned because there was no significant advantage over plasmin alone. Again, no significant undesirable reactions were observed. Follow-up in over 90 per cent of the cases has failed to uncover any case of hepatitis.

USE OF PLASMIN FOR INTRAVASCULAR THROMBOSES

With this background of safety in local use, we proceeded gingerly to intravenous injection of plasmin (A & B),[1] with the ultimate purpose of lysing intravascular thrombi. The first cases were in seriously ill or moribund patients; in these, only toxicity and general reactions were studied. Subsequently, the effect of therapeutic doses on the clotting factors of blood was studied. There were definite variations, but no alarming changes in these factors (10). Fibrinolytic and proteolytic activity of the blood was significantly increased in most cases studied. In 2 patients in whom there was no fibrinolysis, high antiplasmin levels were present before treatment.

The only reaction so far observed with intravascular use has been a pyrogenic one, of varying severity. This reaction ranges from a 1-degree rise in temperature without other manifestations, to a moderately severe chill with other manifestations such as nausea and vomiting, dizziness, headache and muscle pain. Hypotension without signs of shock occurred as a complication following use of one lot of plasmin. The evidence available would lead us to believe that the reactions are due to impurities in the activator, since this material itself produces significant reactions. By progressively decreasing the amounts of SK used for activation (from over 1000 units per mg. of plasminogen to 400 units per mg.), the reactions

[1] A = Plasmin (prepared by Merck Sharp and Dohme, West Point, Pa.). B = Plasminogen activated by Varidase before use (prepared by Ortho Pharmaceutical Co., Raritan, N. J.).

TABLE 1

*Leg Measurements (Inches) in G. K., the First Patient Treated for Thrombophlebitis with Plasmin**

Date	Left Leg				Right Leg			
	Foot	Calf	Knee	Thigh	Foot	Calf	Knee	Thihn
1954								
Dec. 17	10½	15	17¾	22½	9	12¼	14¾	17¼
17	*One injection of plasmin*							
Dec. 18	10¼	14¾	16¼	22	8½	12¼	13⅞	17
Dec. 22	9⅝	13½	15⅝	23	8⅞	11⅞	14	17½
Dec. 27	9	13¾	15⅝	22½	8¾	12½	13¾	18¼

* Acute thrombophlebitis occurred while the patient was receiving radiation therapy for carcinoma of the pancreas, and it was progressing rapidly when plasmin was given. Pain was relieved and did not recur. The patient survived four months without further significant change.

were markedly decreased. Using this small amount, some lots of activator caused little or no reaction, whereas other lots caused very severe reactions. The problem of removal of this pyrogen is being actively investigated. No other reactions to plasmin have been observed. There have been no cutaneous, gastro-intestinal, pulmonary or vascular abnormalities, nor any excessive bleeding, following its use. At postmortem examination of patients dying of other diseases, no abnormalities could be found that were due to the plasmin used during life.

Hepatitis has not occurred in any of the patients. Those who did not succumb early from disease were followed for at least four months, and some for as long as three years. Three of these patients received plasmin prepared from a pool which was later known to contain hepatitis virus, yet they did not contract hepatitis.

Forty-two patients with thromboembolic disease were treated with plasmin. Only a few of these received adequate treatment by the standards established in our animal experiments or by our present standards for human subjects. Despite this, in several instances there was a surprising regression of symptoms, as well as objective evidence of lysis of the thromboses. The best results were obtained in venous thrombosis or thrombophlebitis. Seventeen patients with venous thromboses received treatment with plasmin; in 11 of these it was relatively adequate. In 9 patients of this group there was an excellent response, with complete relief of pain, even though not always accompanied by definite, objective evidence of improvement. The effect on leg measurements in the first patient treated (inadequately) is shown in Table 1. The following are 2 examples of good results:

Case 1—**S. L.**, a 54-year-old white woman with multiple metastases from carcinoma of the breast, postoperatively had thrombosis of the iliac vein with marked swelling of the legs of one month's duration (Fig. 1). She was given plasmin on December 28 and 30, 1956 and on January 1, 1957. There was no significant reaction but there was marked regression of the swelling, as shown in Figure 2. There was a decrease of 3 inches in the size of the

FIG. 1.

FIG. 2.

FIG. 1. Legs of Patient S. L. (Case 1) before treatment, December 28, 1956. The wet gauze dressings are on inflamed cut-down incisions.

FIG. 2. Legs of Patient S. L. after treatment with plasmin, January 2, 1957

right leg, and the difference in measurement between the two legs was only half an inch by January 1. She had no further difficulty in this respect after discharge.

Case 2—**E. G.** Even more striking was the result in this 65-year-old white woman who had undergone pelvic exenteration for carcinoma of the cervix on September 28, 1956. Severe thrombophlebitis of the left leg developed on October 6, and of the right leg on October 29. The swelling, edema and inflammation extended into the buttock on the right, indicating extension at least to the iliac vein. In addition she had septicemia (*Candida albicans*) and was bed-ridden. She needed frequent transfusions but all the veins of the arm were thrombosed, so that it was virtually impossible to administer anything intravenously. On November 28, 1956 (over six weeks after the first thrombosis), she received plasmin. By the end of the first treatment, several of the thrombosed veins in the arms were normally patent. She was treated three more times on successive days. At the end of this period her legs were practically normal in size and she was up and around in a walker. She was discharged ten days after treatment. She traveled to her home in Florida and was known to be free of recurrence, three months later.

In another patient with iliac thrombosis following total gastrectomy, definite changes occurred immediately after treatment with plasmin (Figs. 3 and 4). Unfortunately he succumbed to postoperative complications.

In 2 patients plasmin was administered directly into the involved vein. In one there was rapid dissolution of the thrombus, but later recurrence; in the other there was clinical objective improvement. The leg measurements in the second patient (G. W.) are shown in Table 2.

Four patients with thrombophlebitis and pulmonary emboli (clinical criteria) were treated, none with adequate doses. Three of them experienced complete

FIG. 3.

FIG. 4.

FIG. 3. Venogram in patient with thrombosis of the iliac vein, before treatment. Note distention of femoral vein and of collateral vessels. The block was confirmed by clinical signs—great pressure necessary for instillation, and there were leaks around needle.

FIG. 4. Venogram in same patient, four hours after treatment with plasmin. The ease of flow was confirmed by clinical signs, and free flow of infusion without leaks around needle.

relief of the pulmonary symptoms, although 1 later had a recurrence of thrombophlebitis in the leg. A representative case report follows:

M. H., a 42-year-old white woman with metastatic carcinoma of the breast, had had at least 6 attacks of pulmonary embolism from an infected thrombosis of the vena cava, despite adequate anticoagulant therapy. The attacks occurred during the period from February 27 to March 15, 1956. An indwelling polyethylene catheter had been inserted through the femoral vein into the vena cava following adrenalectomies for her metastatic disease. When the nonfunctioning catheter was removed on February 27, a clot surrounded its tip. Dicumarol therapy was stopped. No emboli occurred after the second day of treatment with plasmin. Edema of the legs began to regress after the third day and the legs were practically normal by the fifth day.

In the fourth patient, at necropsy, no significant pulmonary emboli were found, although she had shown all the clinical signs of progressive repeated attacks. She did, however, have metastatic carcinoma and pneumonitis.

Two patients with thromboses of the central vein of the retina showed no objective evidence of lysis following the use of plasmin, although progression of the process was halted and there was improvement in vision.

Thirteen patients with arterial emboli or thromboses were treated with plasmin. In animals, it was necessary to give more plasmin over a longer time for

TABLE 2

*Effect of Plasmin on Leg Measurements (Inches) in G. W., a Patient Who Had Osler-Weber-Rendu Disease Complicated by Thrombophlebitis from a Cut-down in the Right Femoral Artery**

Date	Right Leg			Plasmin (units)
	Thigh	Below Knee	Calf	
1956				
Sept. 14	22¼	17	11	28/000
Sept. 15	21	15	10¼	
Sept. 17	20¼	14	10	28/000
Sept. 18				56/000
Sept. 22	19	13½	9	

* Thrombophlebitis occurred following transfusion and infusion for gastro-intestinal hemorrhage. Very small doses of plasmin were injected distal to the thrombus. There were no hemorrhagic episodes, and lysis obviously occurred, as there was a pronounced decrease in the size of the right leg.

the treatment of arterial thrombi than for venous thrombi. One would expect the same to be true in human subjects. By such standards, none of these 13 patients received adequate treatment. In 9, the material was given intravenously. In most instances there was temporary improvement, with a return of color, an increase in temperature, and in some cases a return of sensation and motion. The following is an example:

R. B., a 60-year-old white woman with rheumatic heart disease, had an embolus of the axillary artery of eight hours' duration when first seen. During intravenous plasmin therapy, her hand and arm improved markedly. They became pink down to the nail beds, pain disappeared and she could move the fingers. However, about two hours after cessation of plasmin therapy, regression set in, and six hours later the arm was back in the original condition—acutely painful, motionless, cold, and mottled white up to the elbow. An axillary arteriotomy was performed. The embolus was found to be free and practically fell out of the vessel; there was no surrounding thrombus. (The same failure of fixation or propagation of clot was seen in a postmortem case after treatment for an embolus.)

We now feel that local instillation of plasmin at operation is the treatment of choice for patients with arterial thrombus. This method was used in 4 patients. The following are 2 of the case reports:

D. K., 57-year-old white woman, had undergone pelvic exenteration with ligation of both internal iliac arteries (Table 3). On arrival in the recovery room, she was found to have a cold, white, motionless right lower extremity, without arterial pulsations. Continuous caudal anesthesia failed to improve the situation, and eight hours after the first operation the femoral artery was explored. A high femoral arteriotomy revealed a firm thrombus; a long clot was removed with some flow of blood. Following this operation there was no improvement in the leg. Caudal anesthesia and heparin were continued. Eight hours later re-exploration was undertaken and plasmin was instilled into the proximal and distal artery through a polyethylene tube. The tube was advanced as the clot was lysed, until a free flow of blood was obtained, both above and below. By this method it was determined that thrombosis extended from the bifurcation of the aorta to the popliteal area. A very

TABLE 3

*Temperature Changes in Both Legs Following Use of Plasmin in Patient D. K., Who Had Thrombosis of the Right Femoral Artery After Pelvic Exenteration, and Later Thrombosis of the Left Artery**

	Temperature (degrees C.)						Venous Pressure (oscillometer, cm.)		
	May 1, 1956, after attempt at embolectomy under caudal anesth.		May 2, 1956, after plasmin						
			2 hrs.		6 hrs.			May 4, 1956	
	Left	Right	Left	Right	Left	Right		Left	Right
Toe	36.4	27.5	29.3	29.5					
Foot	36.4	32.6	32.2	35.4	29.8	32.2	Lower leg	0	7–7.8
Calf	35.0	31.0	33.3	34.6	32.4	35.2	Below knee	0	7–7.8
Low-thigh	34.0	32.8	35.0	35.2					
Mid-thigh	35.2	32.6	36.0	36.4	36.2	26.2		7.8–8.2	8–8.6
Abdomen	38.4	38.4	37.0						
Pulses	All good	None	Femoral only	All good	Femoral and popliteal	All good		Same as on May 2 at 6 hrs.	

* Note the maintenance of the marked improvement in the right leg, but the subsequent lowering of temperature and loss of oscillometric readings in the left leg following development of obstruction on that side.

small residual clot was removed from the suture line of the previous arteriotomy. After return to the recovery room a hematoma rapidly developed in the wound; when the wound was reopened blood was spurting from the needle hole in the artery to a height of 2 or 3 feet. One suture closed this leak, and the patient was returned to the recovery room with good pulsations in the right dorsalis pedis and posterior tibial arteries—better than in the left leg. The temperature changes are shown in Table 3. About six hours later, the same phenomenon developed in the left leg, with pain to the mid-thigh level and typical color and temperature changes. Sympathetic blocks resulted in a lowering of the pain level to the lower third of the thigh. She was given 100 mg. of plasmin intravenously. There was rapid improvement and the pain level was lowered to the foot. The patient died seven days later from nonfunctioning kidneys, a condition which began before treatment with plasmin. At necropsy the right femoral artery was patent throughout but exhibited severe atherosclerosis and a small thrombus on the old suture line (Fig. 5). The left femoral artery was patent without a thrombus, but a hemorrhagic atherosclerotic plaque almost completely obstructed the lumen of the popliteal artery. Good pulsations were present in the right tibial and dorsalis pedis arteries just before death.

H. G., a 45-year-old white woman, had hemiplegia due to postoperative thrombosis of the right carotid artery of three days' duration. Lysis was obtained in fifteen minutes following the use of plasmin, and normal pulsating flow persisted until she died forty-eight hours later from tracheal obstruction due to a hematoma. Maintenance therapy with heparin and Dicumarol had been instituted after lysis of the thrombus.

Two patients with lower femoral popliteal emboli were treated by combined instillation of plasmin and removal of the embolus. In one, the leg was completely restored to normal; in the other, there was temporary marked improvement, but eventually mid-calf amputation had to be performed because of

FIG. 5. Postmortem specimens of right femoral artery of Patient D. K. seven days after lysis with plasmin. Note small recurrent thrombus on suture line from previous arteriotomy.

residual involvement. Prior to the use of embolectomy and plasmin, the amputation would have been at the mid-thigh level.

Two cases of cerebral thrombosis were treated with plasmin (in inadequate dosage) without success.

Two patients with priapism due to thrombosis of the corpora cavernosa were treated with plasmin. One received the plasmin by intravenous injection, with only minimal improvement. The other patient was a 28-year-old colored man with priapism of one month's duration. The plasmin was injected directly into the corpora cavernosa, and there was complete regression of the priapism within thirty-six hours. He has remained in normal condition, with normal erections, during the three weeks of the follow-up period to date.

DISCUSSION

Judging from our results, it would seem that the benefits of plasmin therapy in cases of venous thrombosis range from significant improvement to complete rapid relief, if adequate doses are administered.

Pulmonary emboli, although notoriously difficult to evaluate clinically, respond well to plasmin.

In the treatment of arterial emboli and thromboses, it is necessary to reach a higher concentration of plasmin for a longer time than is possible by intravenous infusion with present materials; but this may be possible in the future with less pyrogenic material. Old emboli will not be lysed by any material at present available; however, circulation will be improved temporarily, probably by lysing the extensions of the thrombus which block the collateral vessels. This will permit delay of operation for necessary preoperative preparation; and perhaps, with prolonged use, sufficient collateral circulation may develop to preserve the limb. After plasmin therapy the emboli lie free in the artery; this is an unusual finding at arteriotomy and makes surgical removal much simpler and less traumatic, with less likelihood of secondary thrombosis. Thrombi, even when very extensive, can be completely and rapidly lysed by local instillation of plasmin. Direct instillation of plasmin before and after embolectomy makes this operation easier, and may cause lysis of distal thromboses which would prevent a satisfactory result.

Other investigators have suggested that equally good results can be obtained by using streptokinase (SK) alone or pyrogenic materials, to activate the plasminogen in the patient's own blood. Streptokinase is a satisfactory activator, but there is an additional complicating factor when it is used alone. The inhibitor of SK is at a fairly high level in many patients and must first be used up. This is not true in the case of plasmin. It is also conceivable that in many patients more enzyme will be needed than is present in the blood stream. Furthermore, much less SK is necessary for activity when using plasmin than when SK is used alone. Because of the difficulty in obtaining nonpyrogenic SK, its use in large quantities is wasteful. Pyrogenic reactions are undesirable and we should like to be completely rid of them rather than use them purposely for treatment. The effect of plasmin is not dependent upon the pyrogenic reaction, since equally good objective (*in vivo*) fibrinolysis and clinical response have been obtained in patients who do not manifest pyrogenic reactions (10).

Re-thrombosis after partial lysis is a possibility under our present treatment schedules, and until better fibrinolysin is available it may be desirable to treat these patients with anticoagulants after the use of plasmin. We are just beginning to explore this possibility, because of early fear that complications such as hemorrhage would arise. We now feel it is safe to try the combination judiciously, though there is still danger of a result such as that in the patient with carotid thrombosis (H. G.).

At present our main efforts are being directed to the development of a less pyrogenic material. Several approaches are being used. One is the search for other, better activators; some are being tried at present in patients. The second is

purification of SK in order to remove the pyrogens before activation. A third is the removal of the pyrogens after activation of the plasmin.

We have not yet treated thrombosis of the coronary arteries in human subjects with plasmin, because of the toxicity of the material available. However, animal investigations are progressing satisfactorily.

Cerebral thrombosis is such a difficult problem, both clinically and experimentally, that we have made no advances regarding the effect of plasmin in this condition. We hope others will investigate this field.

SUMMARY

Forty-two patients, 17 with venous thromboses, 13 with arterial thromboses or emboli, 4 with pulmonary emboli, and 8 with cerebral or other forms of thrombosis, have been treated with injections of plasmin.

Success has been greatest in venous thromboses, and with direct instillation into arterial thromboses and emboli. In the few cases of pulmonary emboli studied there appeared to be a favorable response.

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THE TREATMENT OF ANEMIA*

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Since anemia is only a symptom, treatment is necessarily directed to the correction of the underlying cause. This discussion is possibly best initiated by classifying the anemias morphologically into macrocytic, normocytic and hypochromic microcytic types.

In general the macrocytic anemias are seen when there is a deficiency of vitamin B_{12} or folic acid.

The normocytic anemias are usually seen in conditions associated with sudden blood loss, acute or chronic blood destruction, lack of blood formation due to toxic exposure, inflammatory, malignant or renal disease, or replacement of the marrow by space-occupying lesions.

Hypochromic microcytic anemia is usually seen when a deficiency of iron exists, either because of lack of iron in the diet, defective absorption of iron, excessive demand, or chronic blood loss. It is also seen in Mediterranean anemia.

THERAPEUTIC AGENTS

Liver extract

I should first like to discuss the specific substances which are available for the treatment of the macrocytic anemias. Liver extract formerly was used for the treatment of this group, but in general its place has been taken by vitamin B_{12}, which is now not only less expensive but also is less likely to be associated with local discomfort at the site of injection. There is an almost complete absence of allergic reaction to vitamin B_{12}. It is given intramuscularly in dosages of from 30 to 100 micrograms per month for maintenance in pernicious anemia, sprue and many cases of nutritional macrocytic anemia.

Folic acid

Folic acid is not used now for the treatment of pernicious anemia because the hematologic results are often not optimal and, more important, the neurologic disturbances are frequently not improved and may actually become worse. However, it is useful in the treatment of sprue, nutritional macrocytic anemia, celiac disease, megaloblastic anemia following intestinal operations, the macrocytic anemia of pregnancy, and the macrocytic anemia of infancy. The oral dose is usually 5 to 30 mg. daily, but it may be given parenterally if circumstances warrant.

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Folinic acid

Citrovorum factor or folinic acid has uses similar to those of folic acid and may be given in dosages of 10 mg. per day orally or 2 to 6 mg. daily intramuscularly.

Vitamin B_{12}

Without question the most important recent advance in the treatment of the macrocytic anemias is the discovery of vitamin B_{12}. The parenteral route is considered by most to be the method of choice for administration of this vitamin, although it is effective when taken by mouth in relatively large doses. There are certain practical advantages in having the patient take B_{12} parenterally, in that he is more likely to remain under observation, he is less likely to omit therapy, and the total expense involved is less than when the oral preparation is used. It can now be said with certainty that in pernicious anemia vitamin B_{12} not only affects the anemia but also the neurologic manifestations. Vitamin B_{12} with intrinsic factor is effective when given orally in pernicious anemia; the intrinsic factor has been shown to potentiate the absorption of B_{12} in the alimentary tract.

Before entering on a discussion of the specific therapy for iron-deficiency anemia, it should be emphasized that the finding of hypochromic anemia in a male patient should call forth a concerted effort to locate the site of blood loss, for this is almost the only cause of hypochromic anemia in the male. This is not to say that a similar search should not be made in the female patient with this disorder. In the female, the source of blood loss is usually in the genital tract; however, if careful history does not suggest this source, examination of the stool for blood, and x-ray examination of the gastro-intestinal tract are definitely in order.

Iron

Iron is a specific for the treatment of iron-deficiency anemia and may be given orally, intravenously or intramuscularly.

In the usual therapeutic doses given to the anemic iron-deficient patients, the absorption of ferrous salts is considered to be 10 to 15 per cent in contrast to an absorption of 1.5 to 3 per cent for iron and ammonium citrate, and 0.5 to 1 per cent for reduced iron (1). In adults, two tablets of ferrous sulfate (0.2 Gm. each) or of ferrous gluconate (0.3 Gm. each) are given three times daily after meals, for a total daily dose of 220 to 440 mg. of iron. Ascorbic acid has been shown to increase the absorption of iron through its capacity to maintain iron in the reduced state, but this has little practical value because of the efficacy of iron alone.

Administration of *hydrochloric acid* may occasionally be useful in aiding the absorption of iron taken orally. It is likewise of some benefit in the occasional patient with pernicious anemia in whom the gastro-intestinal symptoms persist after effective specific therapy. It may now be given in capsule form as glutamic-

acid hydrochloride; this avoids the previous cumbersome method of sipping dilute hydrochloric acid through a straw.

Intolerance to oral administration of iron is often avoided by starting the therapy gradually and by giving it always after meals. Some patients seem to tolerate the gluconate better than the sulfate, although with others it is the reverse. Toxicity is not a serious problem, for the toxic dose is approximately fifty times the therapeutic dose; however, symptoms of abdominal discomfort, nausea, vomiting, diarrhea and constipation lead some patients to discontinue this form of therapy.

The amount of iron which is absorbed daily by the iron-deficient patient is about 20 to 60 mg. This allows red cell production to increase to about twice normal. Reticulocytosis occurs in five to ten days after the beginning of therapy and hemoglobin values increase perceptibly in two to three weeks.

The usual reason for failure of response are: 1) incorrect diagnosis, 2) continued excessive blood loss, 3) the presence of a complicating disease such as infection or uremia, 4) failure of patient to take the medication, and 5) lack of absorption of the ingested iron.

Iron must be continued after the anemia has disappeared, so that the tissue iron stores can be replenished. Thus it is apparent that many months of treatment are required (2).

Indications for parenteral iron therapy are:

1. Intolerance of all iron. Various preparations of iron for oral use should first be tried before a patient is considered to manifest intolerance, and it is essential that the oral tablets be taken *after* meals.

2. Gastro-intestinal disease which may be adversely affected by oral iron—such as ulcerative colitis, gastric ulceration or regional enteritis.

3. The creation of iron stores. This is especially important in patients who may be expected to have future bleeding episodes, *e.g.*, those with esophageal varices, peptic ulcer, or hereditary capillary telangiectasia.

4. Poor absorption of iron. This is very rare and is almost always associated with sprue.

5. Iron-deficiency anemia late in pregnancy. In these instances there is need for quick restitution of iron stores.

It is possible to replenish iron stores by blood transfusion, as 250 cc. of red blood cells contain approximately 270 mg. of iron.

Saccharated oxide of iron is the most widely used parenteral form, and is usually given intravenously in doses of 50 to 200 mg. The total dosage necessary for any given patient may be calculated by the use of the following formula:

$$(\text{Normal Hb} - \text{Initial Hb}) \times 0.255 = \text{Gm. of Fe required.}$$

The deficit usually lies between 1,500 and 3,500 mg. in a 70-kilogram adult. It is usual first to give a course of 500 mg. Then either satisfactory increase in reticulocytes or a rise of 2 Gm. in the level of hemoglobin in three weeks is taken as an indication that the dosage should be continued to the point of full replacement.

The parenteral iron preparation (in a concentration of not more than 20 mg. per cc.) should be given over a period of three to five minutes. The initial dose should not to exceed 50 mg. If no toxic symptoms occur, the dose may then be increased to 100 mg. and thereafter to 200 mg. Reactions occur following 5 to 35 per cent of injections; they may be local or general.

Local reactions include venous spasm, and the results of local extravasation and extensive diffusion of the iron saccharate into the tissues when proper venipuncture is not performed.

General reactions may be: 1) mild, such as flushing of the face, weakness, lightheadedness, headache and drowsiness; 2) moderate, such as general muscle soreness, severe lumbar pain, abdominal cramps, nausea, vomiting, diarrhea, severe headache, vertigo, lacrimation, chills and fever; and 3) severe, such as cough, dyspnea, chest pain, tachycardia, sweating, low blood pressure, syncope and shock.

Chronic iron toxicity can be avoided by never giving more than 5 Gm. of saccharated iron in any one course of treatment, and thereafter verifying the status of iron stores by examination of the bone marrow before continuing treatment. Coleman, Stevens and Finch have illustrated the amount of hemosiderin (iron) in normal sternal marrow, and have shown in their photomicrographs the absence of hemosiderin in the marrow of the iron-deficient patient (3).

Nissim (4) studied the toxic reactions which occur after intravenous administration of saccharated iron oxide, and divided them into two groups—early and late. He believes that the early reactions, such as pain in various regions of the body, symptoms of sympathetic and parasympathetic stimulation, and circulatory collapse, are secondary to individual sensitivity to the impurities in commercial sucrose; whereas the delayed reactions, such as dizziness, weakness, rigors, fever, vomiting, urticaria and collapse are due to the gradual precipitation of the compound in the tissues, especially in the lung capillaries. He warns that care should be taken in using this material in arteriosclerotic patients and especially in those whose lung capillary bed is reduced by disease.

A preparation which has been reported to be less toxic is a dextran-iron complex which is given intramuscularly (5, 6). The intramuscular injection of iron-dextran may be followed by symptoms of tightness in the chest, nausea, fever, headache, diplopia and blurring of vision. Nissim reported (7) that administration of large doses of iron-dextran *intravenously* into adult male mice resulted in deposition or iron in the testes, resulting in atrophy and decreased spermatogenesis. It appears that iron-dextran intramuscularly is generally less likely to cause reactions than saccharated iron intravenously. It may stain the skin, however, if care is not exercised to insert the needle into the muscle deeply along a Z-shaped track.

Cobalt

The use of cobalt in anemia had been under study for some time and it is the general experience that it has little if any value in the management of anemia (8). Cartwright (8) is of the opinion that cobalt in doses of 100 mg. per day will

alleviate the anemia of nephritis and infection, but since its toxicity has yet to be determined he does not favor its use as an established therapeutic agent. Occasional instances of its usefulness in erythrocytic hypoplasia (9) and "pure red cell aplasia" have been recorded (10). The administration of cobaltous chloride for several months has not infrequently been associated with thyroid enlargement and depressed thyroid function (11–13).

Splenectomy

Splenectomy has been used for many years for the satisfactory treatment of congenital hemolytic jaundice and for idiopathic thrombocytopenic purpura It has also been used for the treatment of hemolytic anemia, although it is now recommended only in those patients in whom steroid therapy has proved to be of no value. More recently, splenectomy has been reported to be of benefit in selected patients with Mediterranean anemia; a striking reduction in transfusion requirements was observed. Smith *et al.* (14), in a study of a group of selected patients aged 4 to 18 years, found in general that the older the patient the better the results of splenectomy. In none of these instances, however, was the basic intracorpuscular defect altered.

Miscellaneous

Anemia in Hodgkin's disease, leukemia and related conditions is effectively relieved by the use of therapy directed at the fundamental process. X-irradiation, P^{32}, steroid therapy, and chemotherapeutic agents such as Myleran, nitrogen mustard, triethylene melamine, amethopterin, 6-mercaptopurine and chlorambucil all contribute to the alleviation of the anemia so commonly associated with these diseases.

Tocantins and Wang (15) recommend the use of radioactive colloidal gold (Au^{198}) in patients with severe acquired auto-immune hemolytic anemia which does not respond to splenectomy and to steroids. The dose suggested by them is 10 to 20 millicuries intravenously repeated in two to three months. It is not given in the presence of thrombocytopenia or recitulocytopenia.

Desiccated thyroid is a specific for the treatment of the anemia of hypothyroidism, which will respond to no other agent. It is axiomatic that if a patient with macrocytic anemia fails to respond to vitamin B_{12}, his thyroid status should be evaluated forthwith.

In general, transfusions should not be given unless the nature of the underlying disorder is understood. When, because of a dangerous degree of anemia, transfusion is mandatory, a hemoglobin determination, red cell count, reticulocyte count and blood smear should first be obtained. Transfusions must be used with great caution in hemolytic anemia because reactions are not infrequent; washed red-cell transfusions are to be preferred. In severe acute blood loss and in patients with a hemoglobin level below 5 Gm. per 100 ml., immediate transfusion is essential following the initial studies described. In chronic aplastic anemia it is usually advisable to maintain the hemoglobin at a level of 9–10 Gm. per 100 ml., which is usually sufficient for moderate activity. Transfusion of

packed red cells has an advantage in the severely anemic patient in whom one wishes to raise the blood volume least.

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CONTROL OF SERUM CHOLESTEROL BY EXPERIMENTAL DIETS*

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Atherosclerosis, believed now to be our No. 1 killer, has drawn great interest not only from the laboratory and the clinician, but from the public as well. It is being recognized that arteriosclerosis is the most common disease in the Western World. Arteriosclerosis in this case refers to that vascular disease of the intima in which a lipid-containing deposit encroaches upon the lumen and thus diminishes the blood flow.

Control of this disease process has become vastly more important in clinical medicine since it has been shown that 90 per cent of coronary thromboses are caused by atherosclerosis (1).

Studies of atherosclerosis in various parts of the world have revealed that climate, locale, and racial characteristics are not the greatest factors producing atheromatous lesions; these are important only to the extent that they affect the available diet of these people. Diet is now believed to be one of the greatest etiologic factors.

The disease seems to follow higher economic levels, more than would be expected by chance, and the incidence among poorer classes of people is distinctly less than among those who enjoy a higher standard of living.

In association with the increased incidence of coronary artery disease from atherosclerosis there has been found an increase in the concentration of serum cholesterol, whereas in people with a low incidence of atherosclerosis the opposite is true (2).

The recent work of Bronte-Stewart and associates of Capetown (3) made it appear that the addition of vegetable or marine-animal fat (unsaturated fat) to the diet would be sufficient to maintain the serum cholesterol at a lower level and thereby reduce the atheromatous deposits causing generalized atherosclerosis.

We selected several patients with long-standing high levels of serum cholesterol for study. Following addition to their daily food intake of 4 ounces of unsaturated vegetable fat the cholesterol levels were definitely reduced. The reduction was only temporary, however. Later studies showed a rebound to almost the previous level, despite continuation of vegetable oil.

Re-examination of the original work conducted at Capetown (3) showed that the diets had to be maintained with a low total fat intake as well as a great reduction in animal fat or saturated fat. Therefore, we proposed to conduct further studies along this line. Several investigators had previously maintained that a high intake of animal fat accounted for the general increase in atherosclerosis (4), and this was made the basis of our study. One of our mistakes in the

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beginning was to give too much neutral unsaturated oil, thereby increasing the total fat intake.

METHODS AND PATIENTS

On all patients studied, a history was taken which furnished a general idea of the percentage of total fat and of animal fat in the diet. Diets were then prescribed for reducing the intake of animal fat. The intake of total fat was restricted to approximately 20–25 per cent.

A general plan of treatment was set up, using diet as the main factor. Patients were selected for study who had signs or symptoms of atherosclerosis, who had suffered an attack of coronary thrombosis or cerebral thrombosis, or who had a serum cholesterol level of 300 mg. per 100 ml. or over.

In addition to dietary control, an unsaturated vegetable oil was to be ingested, in any form desired. Soybean oil was finally chosen after trying peanut, corn, cottonseed, and olive oil. Soybean seemed to have the necessary qualifications—high iodine value (132.6) and a higher percentage of di- and triethanoid acids (linoleic and linolenic acids) than any of the other available oil (5). The dosage was 1 tablespoonful daily.

The prescribed diet is shown in Table 1.

Hydrogenated fat was eliminated for the following reason. It is made up of a vegetable oil which initially was unsaturated but has been saturated or partially saturated by removal of some of its double bonds in the process of hydrogenation. In this process also may be formed some trans-fatty acids with a bizarre molecular structure, which may add to the difficulty of utilization of these fats.

Little attention was paid to the non-fat cholesterol content of food, since the body can endogenously produce many times the total amount of cholesterol ingested in food daily in its process of transportation of fat (7). Attention was focused instead on fat content.

This work was conducted on private office patients with the exception of 2 chosen from the Garfield Hospital Cardiac Clinic. All patients were white except the 2 from the clinic, and were of varying ages, social status, and economic levels. Seventeen were male and 21 were female. Under these circumstances the

TABLE 1

Diet

Meat—Lean cuts of beef, lamb, veal, chicken or turkey (skin removed).
Fish—Fresh or frozen.
(All meat and fish broiled, boiled, or baked, but not fried.)
Limited:
Cheese (except dry-curd cottage cheese), eggs, whole milk, cream, butter. (Salad oils allowed in small amount.)
Omitted:
Pork, fried foods, re-use of dripping fat, hydrogenated fats, margarine, cream soups, cream sauces, gravies, whipped cream, ice cream, certain bakery cakes and mayonnaise.
Soy Bean Oil—½ ounce, in any way desired daily.
Total fat estimated as 20 to 25 per cent.
Diet must be isocaloric and weight must be maintained at a constant level (6).

clinician is entirely dependent on the integrity of the patient, and studies are not so easy to conduct as in a hospital, or when food is controlled by a dietitian.

RESULTS

The study started with 48 patients, but 10 were unable or unwilling to continue. Some with digestive problems were unable to take the soybean oil. Others were elderly or became disinterested.

In the 38 patients finally studied under the foregoing dietary regimen, the average initial serum cholesterol level was 358 mg. per 100 ml. The highest value was 444 mg. per 100 ml., and in 10 patients the level was over 400 mg. per 100 ml. The average fall in the serum cholesterol level was 25 per cent. In 20 of the 38 cases the reduction was more than 25 per cent. The study was conducted over a period of nine months, and the average length of study per patient was 5.4 months.

From a study of dietary history, certain patients seemed to have high serum cholesterol levels despite a low fat intake. Five such patients were treated with soybean oil alone, using the prescribed dosage. Cholesterol studies were made at three-week to one-month intervals. The results are shown in Figure 1. The serum cholesterol values reached normal or even subnormal levels.

Some interesting facts were brought out in this study. Diets were started at different times through the summer and fall of 1956. When there was success in lowering the serum cholesterol level, it seemed to act as an incentive to continue. However in some patients the dietary schedule was disrupted by rich Christmas foods, as confirmed by subsequent cholesterol values. A typical example is shown

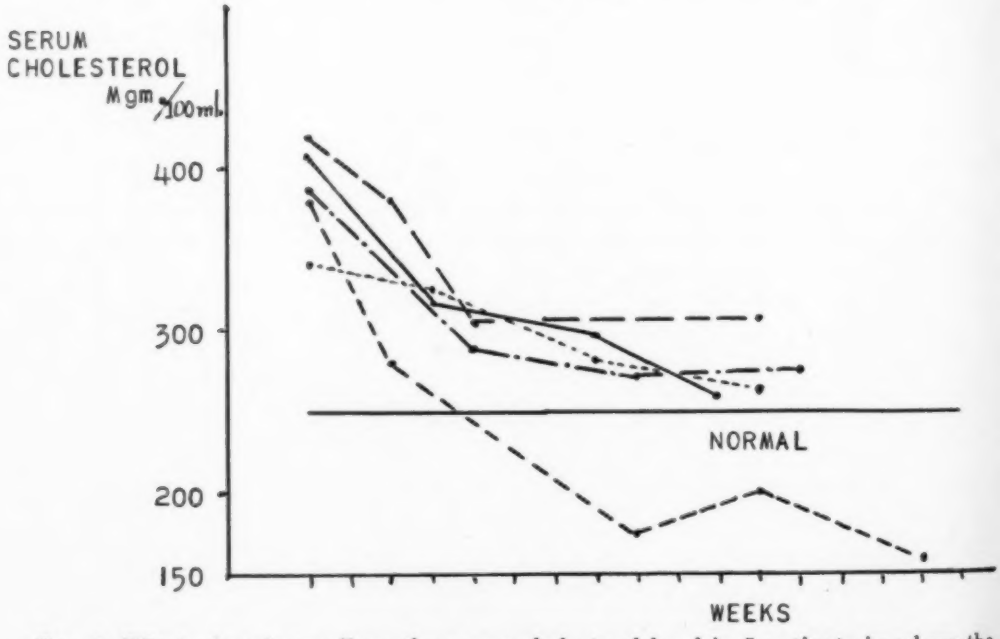

FIG. 1. Effect of soybean oil on the serum cholesterol level in 5 patients in whom the cholesterol values were high in spite of a diet low in fat.

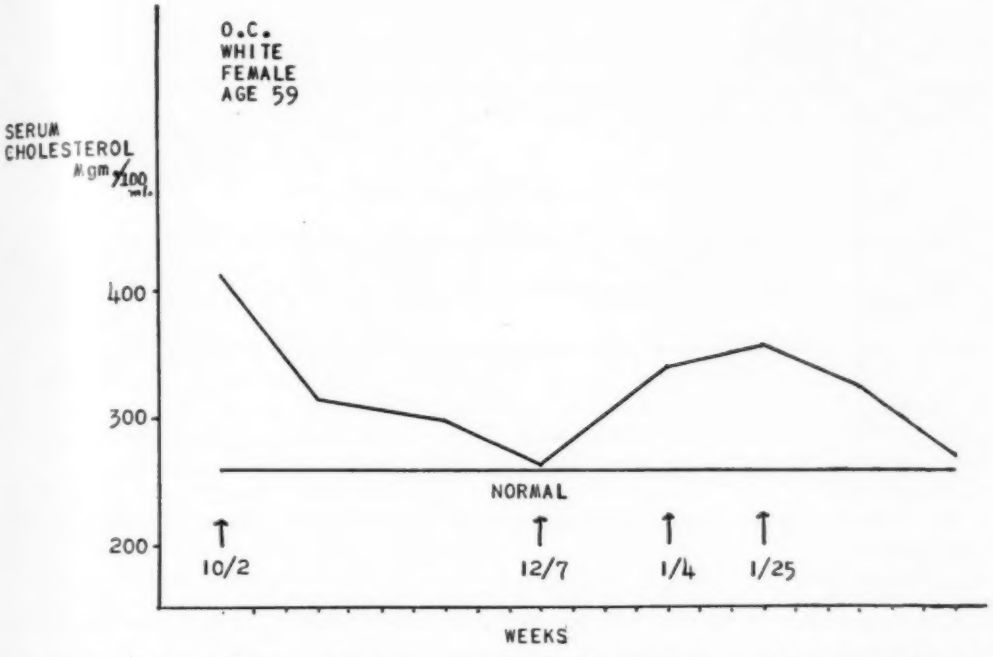

FIG. 2. Effect of Christmas-season escape from diet on the serum cholesterol level in a 59-year-old woman.

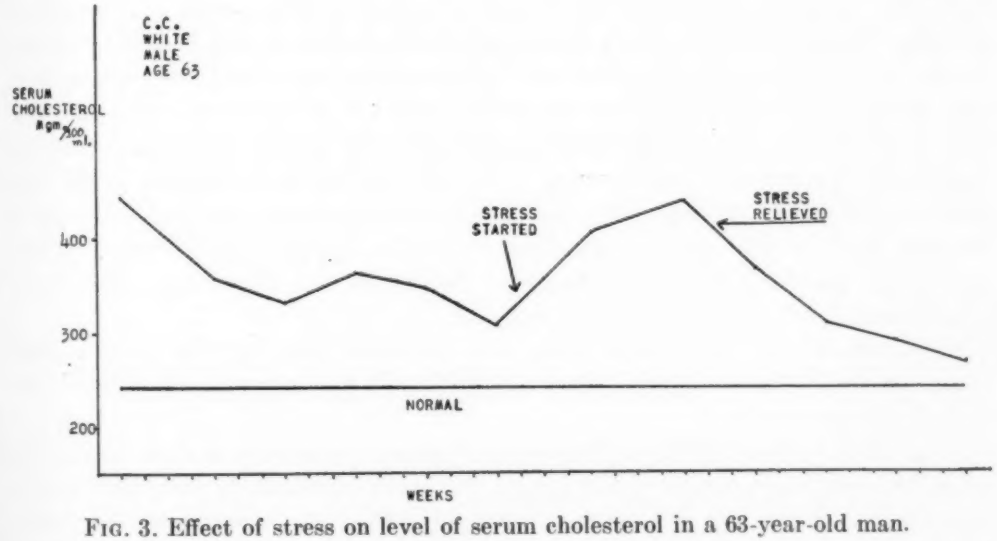

FIG. 3. Effect of stress on level of serum cholesterol in a 63-year-old man.

in Figure 2. Just before Christmas this female patient's cholesterol reading was normal. The first determination after Christmas showed a definite rise. The Christmas dietary habit-pattern was not broken until some weeks later. Then the serum cholesterol level again returned to normal.

It was also noted that periods of stress were accompanied by a definite rise in the concentration of serum cholesterol despite all attempts at control. An example

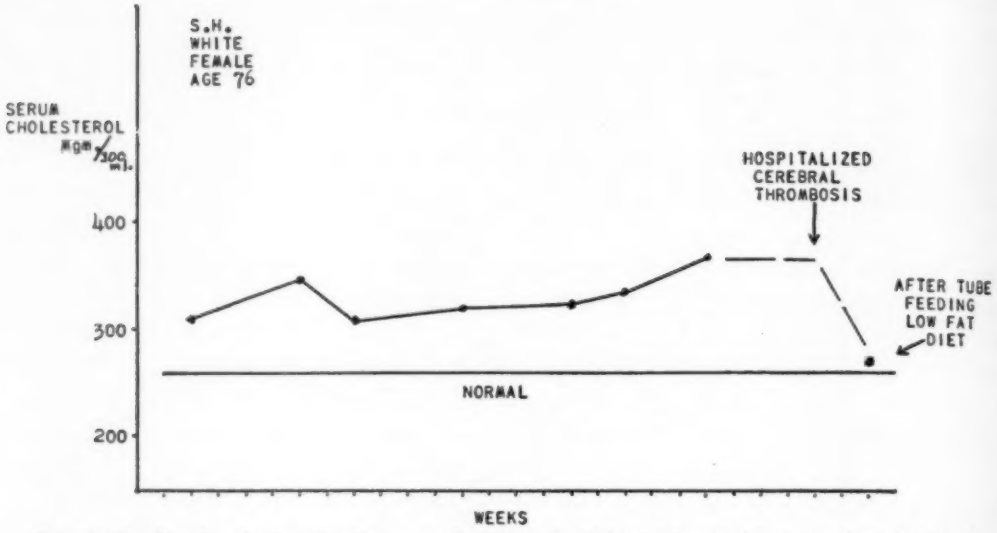

FIG. 4. Reduction in level of serum cholesterol achieved by rigid control of fat intake (tube feeding).

is shown in Figure 3. In this 62-year-old man, when the period of stress was over, the serum cholesterol returned to its former level or even lower.

When diet is followed strictly enough and a low fat intake is maintained, the serum cholesterol concentration can be brought to a desired level. Figure 4 shows the course of the serum cholesterol in a 76-year-old woman who had had two previous attacks of cerebral thrombosis. The second attack had left a slight speech defect and unsteadiness of gait. However she was able to live alone. She was interested in our study, but apparently did not comprehend what she was told in the many conferences which were held. The serum cholesterol concentration never dropped to the normal level, and it reached its highest point just prior to the third cerebral thrombosis. When hospitalized, she had to be tube fed and the diet was made to conform to the fat intake recommended to her during the previous five or six months. Then only did the serum cholesterol concentration fall to nearly the normal level.

In the whole series of patients there was general improvement in physical well being. In some there was improved circulation in the extremities. Others just looked and felt better.

Some did not respond as rapidly as others, and considerable time had to be spent re-educating them in eating habits. Several consultations were held before they learned the proper procedure in controlling the diet. Newspaper and magazine publicity was helpful in stimulating interest and enabling some of these patients to attain a good result.

SUMMARY

Thirty-eight patients with hypercholesterolemia were studied while receiving a diet low in animal and total fat, with an added ration of unsaturated vegetable oil. There was an average reduction of 25 per cent in the level of serum cholesterol, and in 20 of the 38 patients the reduction was greater than 25 per cent.

Acknowledgments

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SURGICAL VERSUS MEDICAL THERAPY IN ACUTE ABDOMINAL CONDITIONS*

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This report concerns a study of 1,000 adult patients admitted to four different hospitals because of acute abdominal complaints. They were seen and examined by various physicians ranging from internes and admitting physicians to the chief surgeon. All these patients manifested signs and symptoms sufficiently pronounced to justify admission to a hospital with a diagnosis indicating some acute condition within the abdomen.

The distribution of the admission diagnoses was as follows:

	No. of Cases
Acute appendicitis	456
Pelvic pathology	155
Perforated peptic ulcer	107
Acute cholecystitis	56
Lesions of the colon	45
Pancreatic diseases	37
Small-bowel obstruction	34
Large-bowel obstruction	29
So-called primary peritonitis	26
Mesenteric vascular occlusion	15
Traumatic injuries to abdomen	15
Acute physiologic disorders	14
Neurologic diseases	11

From this tabulation it is evident that the most frequent admission diagnosis was acute appendicitis. Not all of the 456 cases with this diagnosis proved to be acute appendicitis; however 90 per cent of them were subjected to surgery. Contrariwise, of the 155 cases with a diagnosis of pelvic pathology, only 50 per cent were subjected to surgery. In this discussion the term surgery is used to indicate an emergency surgical procedure. Many of the patients did not undergo operation on the day of admission, but were studied and treated surgically at a later date. All the 107 patients in whom the diagnosis was perforated peptic ulcer were operated upon as emergency cases. (Incidentally, the diagnosis in this group of patients was correct in 101 of the 107 cases.) Closure of the perforation was the only procedure performed, and there was no mortality. The pathologic lesion most often confused with perforated peptic ulcer was acute cholecystitis. A diagnosis of acute cholecystitis was considered sufficient justification for immediate

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surgery if the patient was acutely ill for not more than twenty-four to thirty-six hours; after that period the records show that conservative medical therapy was chosen. In most instances the patient was advised to return in about eight weeks for study of the gall-bladder; elective surgery was carried out if calculi were visible in the roentgenogram.

Appendicitis, pelvic pathology, perforated peptic ulcer and acute cholecystitis, were the disease processes for which immediate operation was most frequently performed. In the remaining categories, with one exception, the frequency of immediate surgical intervention fell rapidly, although delayed surgery was often indicated after adequate studies were performed. The only exception to this rule was the group of penetrating abdominal injuries. Whenever the abdominal wall was pierced because of injury, operation was performed immediately. On the other hand, when an acute physiologic disorder or a neurologic disease was suspected, surgery was contraindicated as an emergency procedure.

A sub-classification of the admission diagnoses, according to the various disease entities found after study or surgery was as follows:

I. Acute Appendicitis
   - Acute mesenteric adenitis (2 cases, Hodgkin's disease)
   - Right renal pathology (mostly calculi)
   - Acute gastro-enteritis
   - Meckel's diverticulitis
   - Pelvic inflammation
   - Ileo-cecal disease
   - Segmental ileitis

II. Pelvic Pathology
   - Ruptured corpus hemorrhagicum
   - Ectopic pregnancy
   - Salpingitis or hydrosalpinx
   - Twisted ovarian cyst or fibroid
   - Segmental ileitis

III. Perforated Peptic Ulcer

IV. Acute Cholecystitis

V. Lesions of the Colon
   1. Cecum and ascending colon:
      - Neoplastic diseases
      - Tuberculosis (1 case)
      - Secondary cecal perforation
      - Diverticulitis
   2. Descending colon and rectosigmoid:
      - Acute diverticulitis (with or without perforation)
      - Perforation of ulcerative colitis
      - Perforation secondary to carcinoma
      - Acute sigmoiditis (1 case)

VI. Pancreatic Diseases
   - Acute pancreatitis (50% by surgical exploration)
   - Traumatic pancreatitis (following gastrectomy)
   - Pancreatic calculi (2 cases)

VII. Small-bowel Obstruction
   - Atresia and stenosis
   - Malrotations (volvulus)

Herniae of all types
Postoperative adhesions
Gall-stones in small bowel
Segmental ileitis
Neoplasm of ileum (1 case)
Intussusception (1 case)

VIII. Large-bowel Obstruction
Fecal impaction (especially in elderly)
Carcinoma
Volvulus
Intussusception
Conditions confused with intestinal obstruction
Congenital megacolon
Ascites
Large ovarian cyst
Reflex paralysis of colon

IX. So-called Primary Peritonitis
Pneumococcal peritonitis
Streptococcal peritonitis
Tuberculous peritonitis (1 case)
Abdominal signs in rheumatic fever

X. Mesenteric Vascular Occlusion (all cases subjected to surgery)

XI. Traumatic Injuries to the Abdomen
Penetrating wounds
Non-penetrating wounds
Subparietal rupture of intestine due to muscular effort (1 case)
Injury to liver, spleen, kidneys
Rupture of urinary bladder
Retroperitoneal hemorrhage
Ingested foreign bodies

XII. Acute Physiologic Disorders
1. Metabolic disorders (diabetes, uremia, Addison's disease)
2. Blood dyscrasias (sickle-cell anemia, leukemia, Henoch's purpura)
3. Cardiovascular diseases
4. Gastro-intestinal allergy (serum sickness, black widow spider bite)
5. Infectious diseases (typhoid, pneumonia, measles)
6. Intoxications (alcoholism, lead poisoning)

XIII. Neurologic Disorders
1. Girdle pains of tabes dorsalis
2. Herpes zoster
3. Intercostal neuralgia
4. Compression of spinal nerve due to disorder of spinal column.

COMMENT

The following surgical philosophy has been our cardinal principle: correct diagnosis is not essential to correct treatment. When a sincere effort has been made to arrive at an accurate diagnosis and it has been fruitless or equivocal, the next important decision is whether or not the patient presents a surgical problem. If there be a surgical problem, then it must be decided whether or not immediate operation is in order. If operation is to be immediate, the next step is to determine the operability of the patient. Can he tolerate major surgery? When the surgeon is forced to make a choice, correct evaluation of operability may be preferable to correct diagnosis, so far as the life of the patient is concerned.

SURGICAL TREATMENT OF CARCINOMA OF THE PANCREAS*

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It has now been twenty-three years since Allen O. Whipple performed the first successful pancreatoduodenal resection on a patient with carcinoma of the ampulla of Vater. Following this report there was marked interest in pancreatoduodenectomy in the treatment of carcinomas arising in the region of the head of the pancreas. As might be expected for a new procedure which required resection of part of the pancreas, part of the common duct, part of the stomach, and all of the duodenum, the operative mortality was high. Five years ago, in 1952, there were reports in the literature concerning 13 patients who had survived five years or more after the Whipple-type of operation for carcinoma of the head of the pancreas, the ampulla or the papilla (1). A year ago Dennis and Varco found the number of survivors as reported in the literature to be 26 (2). Many physicians, therefore, concluded that the high operative mortality and the relatively few five-year survivors indicated that the Whipple operation was not a justifiable procedure. In the light of this background we should like to review our experiences at the Hospital of the University of Pennsylvania during the period May 1942 to May 1952, and to discuss some of the essentials of diagnosis and the major factors in surgical therapy.

CARCINOMA IN THE REGION OF THE HEAD OF THE PANCREAS

Carcinomas of the region of the head of the pancreas include tumors arising from the pancreatic acini, pancreatic ducts, the pancreatic portion of the common bile duct, the ampulla of Vater and the papilla. These lesions are considered as a group because preoperatively and also at the time of operation it is usually not possible to demonstrate the exact origin of the lesion.

Signs and symptoms

It is most important to realize that very few of these patients follow the generally accepted interpretation of Courvoisier's law when the disease is in an operable state. In other words, prior to a successful pancreatoduodenectomy, few patients with carcinoma in the region of the head of the pancreas have an unremitting, painless jaundice of high degree associated with an unmistakably palpable gall bladder.

The most common signs and symptoms in 25 consecutive patients operated upon by us are listed in Table 1. The early manifestations were those present at the time the patients were ill enough to either quit work or consult their family

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TABLE 1

Percentile Incidence of Signs and Symptoms of Carcinoma in the Region of the Head of the Pancreas (25 Patients)

	Early (%)	At Time Of Operation (%)
Pain	48	72
Jaundice	40	88 (13*)
Anorexia	36	76
Weight loss	24	88†
Indigestion	24	84
Palpable gall bladder	8	50‡

* Intermittent.
† Average loss 19 pounds.
‡ Five previous cholecystectomies.

physicians regularly. Pain, the most common early symptom, was present in 48 per cent of the patients. Jaundice, the next most common symptom, was present in 40 per cent. Anorexia, weight loss, and indigestion were frequently observed. Early in the course of the disease only 8 of the 25 patients had a palpable gall bladder. At the time of operation, however, 72 per cent had pain, 88 per cent had jaundice, 76 per cent had anorexia, 88 per cent had lost weight (average, 19 pounds), 84 per cent had indigestion; and only 50 per cent had a palpable gall bladder. A number of these patients had had previous operations; 5 had had cholecystectomies. Symptoms had been present for two years or thereabouts in several patients before they were subjected to Whipple resection. With a better understanding of this disease, we can establish the diagnosis earlier. The common interpretation of Courvoisier's law is not of prime importance in establishing the clinical diagnosis.

It should be emphasized that positive x-ray findings frequently indicate an inoperable lesion. These include: 1) a widened duodenal loop, 2) the inverted "3" sign in the duodenal contour, and 3) irregularity or distortion of the mucous membrane of the duodenum.

Histologic diagnosis

Frequently at operation it is not possible to obtain a biopsy specimen of the tumor in the head of the pancreas, even with a biopsy needle. The lesions may be as small as 1 cm. in diameter. The head of the pancreas is a very vascular area. In addition, the pancreatic tissue usually shows evidences of pancreatitis in the area immediately surrounding the tumor. In only 42 per cent of our patients were we able to make a definite histologic diagnosis of carcinoma at the time the Whipple resection was performed. This means that in most instances the surgeon had to make a bold decision. At the time of operation every effort should be made to determine the possibility of curing the patient surgically. Frequently an hour or an hour and a half is spent in assessing the extent of the carcinoma before any essential structures are divided. The head, body and tail of the pancreas and the

portal vein can be freed to a considerable extent from the surrounding tissues. The lymph nodes and the viscera of the abdomen are examined very carefully and, when indicated, a biopsy specimen is taken in an attempt to demonstrate tissue invasion or metastases. When there is invasion of, or metastases to structures that cannot be removed, there is no hope of cure and the patient should not be subjected to an operation of this magnitude.

In the past it has been stated that patients with carcinomas of the pancreatic acini and pancreatic ducts should not be operated upon, because few of them survive five years. This is an academic statement, because rarely can the pathologist tell the origin of the tumor by examining a frozen section, with the possible exception of lesions arising from the adjacent duodenal mucosa. In fact, the pathologist often has great difficulty in determining the origin of the lesion when he has the gross specimen and the paraffin sections. This is understandable, for the liver, biliary tract and pancreas arise as pouches of the embryologic gastrointestinal tract.

Types of operation and survival rates

From May 1942 to May 1952, 83 patients with presumed or definite carcinoma of the region of the head of the pancreas were operated upon by a number of surgeons at the Hospital of the University of Pennsylvania. Table 2 lists the operations performed. It may be seen that 12 patients were not subjected to a definitive type of operative procedure; 50 underwent cholecystenterostomy (biliary shunt); and 21, pancreatoduodenectomy (Whipple resection). Modern

TABLE 2

Types of Operation Used in Surgical Treatment of Carcinoma of the Head of the Pancreas (May 1942–May 1952, Hospital of the University of Pennsylvania)

Operation	No. of Patients
Laparotomy	12
Biliary shunt	50
Pancreatoduodenectomy	21
Total	83

TABLE 3

Data on 6 Patients Surviving Pancreatoduodenectomy by 5 to 10 Years

Patient	Site of Lesion	Survival (yrs.)	Evidence of Recurrence	Surgeon
D. C.	Ampulla	5+	No	J. E. R.
M. T.	Common duct	6+	Yes	J. E. R.
G. P.	Common duct	6+	No	H. A. Z.
A. C.	Duodenum	6+	Yes	H. A. Z.
B. D.	Ampulla	7+	No	H. A. Z.
A. R.	Common duct	10+	No	H. A. Z.

therapy dictates that gastroenterostomy be performed in conjunction with cholecystjejunostomy. Many patients are improved by a biliary shunt, only to die of intestinal obstruction.

Seventeen of the 21 patients subjected to pancreatoduodenectomy survived thirty or more days—an operative mortality of 19 per cent. Six patients survived pancreatoduodenectomy by five to ten years. The type of lesion, length of survival, and evidence of recurrence in each patient are shown in Table 3. The five-to-ten-year survival rate was 29 per cent among the 21 patients subjected to pancreatoduodenectomy, and 35 per cent among the 17 patients who survived the operation. Pancreatoduodenectomy or Whipple resection produced as good or nearly as good results as did radical operative procedures for carcinoma of the stomach or esophagus. Five years ago, Walters and Berkson (3) reported an increase from 5 to 14 per cent in the five-year survival rate of patients seen at the Mayo Clinic with carcinoma of the stomach prior to 1916 as compared with those seen prior to 1949. Mustard and Ibberson (4) reported that among 133 patients operated on for carcinoma of the esophagus, 7 were living five years after the operation—a survival rate of 5 per cent. Among our 83 surgical patients in whom there was a presumed or histologic diagnosis of carcinoma in the region of the head of the pancreas, 10 lived more than five years. In 4 of these five-year survivors, the diagnosis was not made histologically, and they were not subjected to pancreatoduodenectomy; but they lived five, nine and a half, eleven and a half, and thirteen years, respectively. Of the patients not subjected to pancreatoduodenectomy in whom the diagnosis of carcinoma was positive, the longest survival was three and a half years. Thus the five-year survival rate for all 83 patients was 12 per cent; for the 21 patients subjected to pancreatoduodenectomy, 29 per cent; and for the 17 patients who survived pancreatoduodenectomy, 35 per cent.

CONCLUSION

In the light of our experiences with pancreatoduodenectomy, we believe that the operation is worthwhile in selected cases.

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THE SUCCESSFUL THERAPY OF FIBROSITIS*

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Rheumatologists, for many years have claimed that fibrositis is an improper name for the non-articular rheumatic disease it designates. Despite its inadequacy, this term has remained in use because of mutual acceptance of its definition and mutual lack of knowledge regarding its pathology (1–4). Fibrositis, by definition, is a non-articular rheumatic disease characterized by aching pain and stiffness occurring with inactivity, relieved by mild activity, salicylates and heat, and recurring with overactivity and fatigue. There are two forms of fibrositis acute and chronic, with different etiologies.

ETIOLOGY

Acute fibrositis is due to the overuse of a muscle, that is, forcing it to do more work than it has been conditioned to perform. This type of disability is often seen in the early stages of pre-seasonal physical training by athletes and after prolonged or strenuous physical exertion (over-fatigue) by persons unaccustomed to such exercise. Acute fibrositis can initiate chronic fibrositis when it is used as an excuse for complete disuse of the affected muscle(s), or if over-fatigue occurs frequently enough to induce muscle atrophy.

After the age of about 40, muscle strength generally declines slowly over the remaining years of life without producing symptoms (Fig. 1). This decline is often based on the traditional belief that as one passes the middle years of life it is necessary to be less active physically if one wishes to live long. This, of course, is not true. When muscle strength falls below the average level of asymptomatic decline, symptoms of chronic fibrositis occur. Aching and stiffness, even though mild and far from disabling at first, are generally considered as danger signs by the patients; whereupon they further limit their physical activity and thereby increase the muscle atrophy and augment the severity and scope of the symptoms. Other manifestations are easy fatigue, decreased strength, and hypermobility, limited motion and instability of joints.

Thus chronic fibrositis is caused by a decrease in muscle strength, bulk and tone designated as atrophy. It may occur because of either disuse, decreased use, or prolonged muscle strain (Fig. 1).

Complete disuse or relative inactivity of a part due to such conditions as bursitis, arthritis or fracture may cause sufficient atrophy to produce symptoms within a few weeks. Decreased use of muscles due to alteration in habits, change from a physically active to a sedentary occupation, "televisionitis," or emotional tension will not produce symptoms for a year or two, since this type of atrophy

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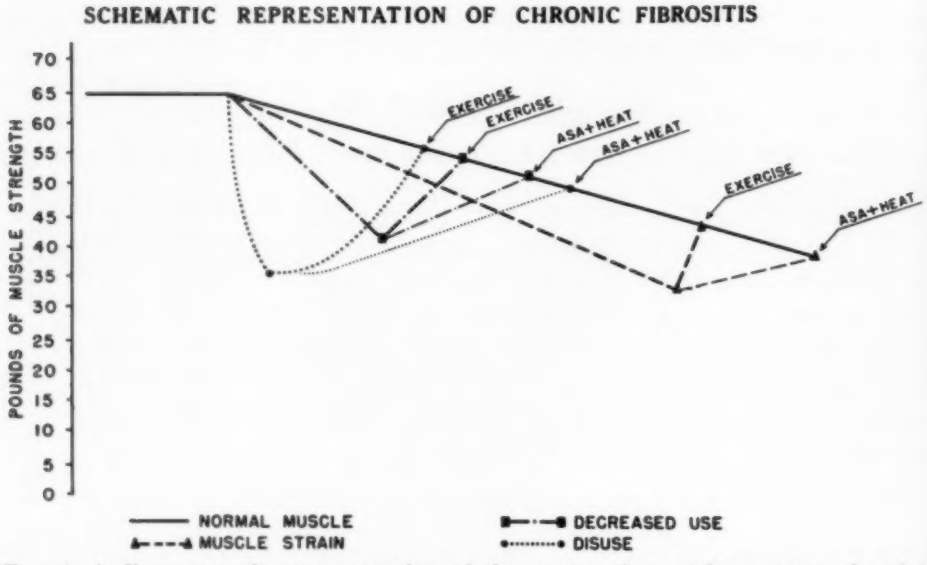

FIG. 1. A diagrammatic representation of the status of muscular energy; the plateau ends at age 40. Thereafter there is a nonsymptomatic decline of muscle strength and tone (sloped solid line). The dotted line represents fibrositis occurring within a few weeks after complete disuse. The dash-dot line represents fibrositis occurring after 12 to 24 months of decreased use. The line of dashes represents fibrositis occurring as a result of muscle strain over many years. In each instance, the response to traditional therapies requiring months of treatment is contrasted with the response to modern therapeutic methods requiring only weeks of treatment.

progresses very slowly. Muscle strain secondary to poor posture, occupational overuse, or physical defects in the musculo-skeletal system takes the longest time to produce symptoms—from five to twenty years or more.

The muscular changes which cause stiffness and aching follow a logical pattern. Normal muscle tonus is the result of slight stretching of the muscle between its origin and insertion, and does not cause fatigue. When atrophy develops, the individual muscle fibers (and therefore the whole muscle) become thin and elongated (Fig. 2). There is actual slackness of the muscle, and consequent loss of the natural involuntary tonus. When a muscle in this condition is called upon to move its joint, there is a slightly prolonged stimulus-reaction time (SRT) (5), since the slack (CA, Fig. 2) must be taken up before the motion (AB, Fig. 2) can occur. Thus, an atrophied muscle must contract through a greater distance (CA + AB) than a normal muscle (AB). This accounts for some of the fatigue complained of by the patients.

As atrophy progresses, the muscle develops tonicity by taking up the slack through partial contraction; this is brought about by failure of the muscle to relax to its full length after the shortening required during the motion of a joint. Such involuntary partial muscular contraction tends to increase when the patient is put at rest, and causes the stiffness or "spasm" known as jelling. The greater the atrophy, the greater the amount of partial contraction required to produce tonicity and the more severe and prolonged the "spasm" or stiffness after inactiv-

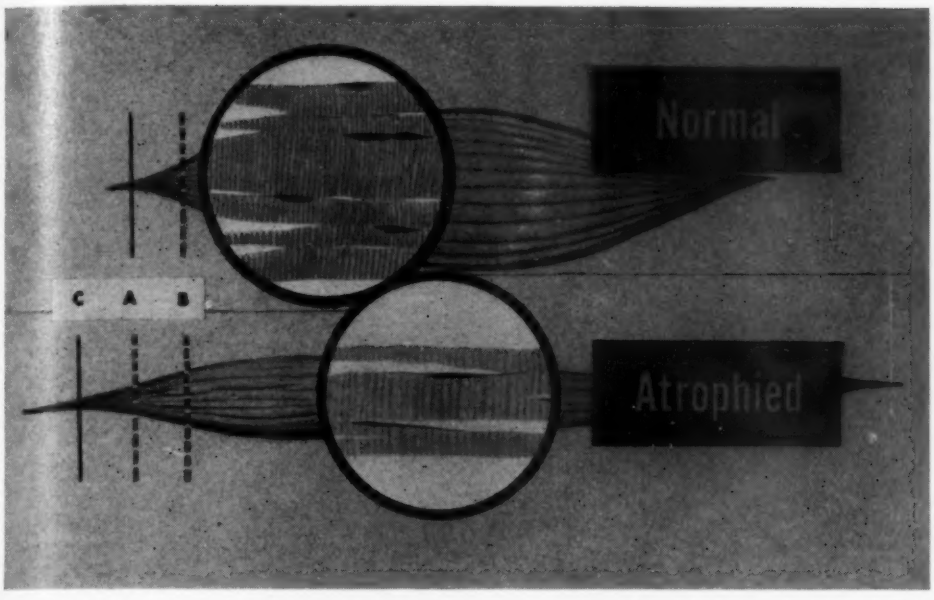

FIG. 2. A diagrammatic representation of normal versus atrophied muscle. **AB** indicates the extent of shortening required to produce motion in the joint. In atrophied muscle, the distance **CA** (due to elongation) as well as **AB** must be taken up by contraction in order to produce motion in the joint. This extra work accounts for the prolonged stimulus reaction time (SRT), as well as for much of the fatigue.

ity. This constant partial contraction of muscle is the source of a major part of the aching and fatigue which is so prominent in this disease.

Patients who have had fibrositic symptoms for weeks or months frequently complain (depending upon the part involved) of inability to make fine movements, dropping of even light-weight objects, or a tendency for a knee to give way. Muscle atrophy and the slower SRT account for these complaints. Careful observation of the patients will reveal that these unpleasant and sometimes dangerous events will not occur if the patient proceeds slowly enough to adapt to the delayed reaction time, thus permitting the muscles to contract. Two very simple experiments demonstrate these findings.

The majority of patients who complain that a knee feels as though it would give way have seldom fallen. When gradually increasing their walking speed, they may suddenly move faster than the SRT, the quadriceps will fail to contract, and the knee will give way. The application of an elastic roller bandage, firmly applied approximately four finger-breadths above the upper pole of the patella, will take up the slack in the muscle, the SRT will be shortened, and the patient will be able to walk at an even faster pace.

This train of events is illustrated diagrammatically in Figure 3. A well conditioned quadriceps muscle is like a rope over a pulley, without slack, ready to lift the weight. The atrophied muscle is comparable to the condition in which the rope is slack. Applying the binder to the muscle is akin to taking the slack out of

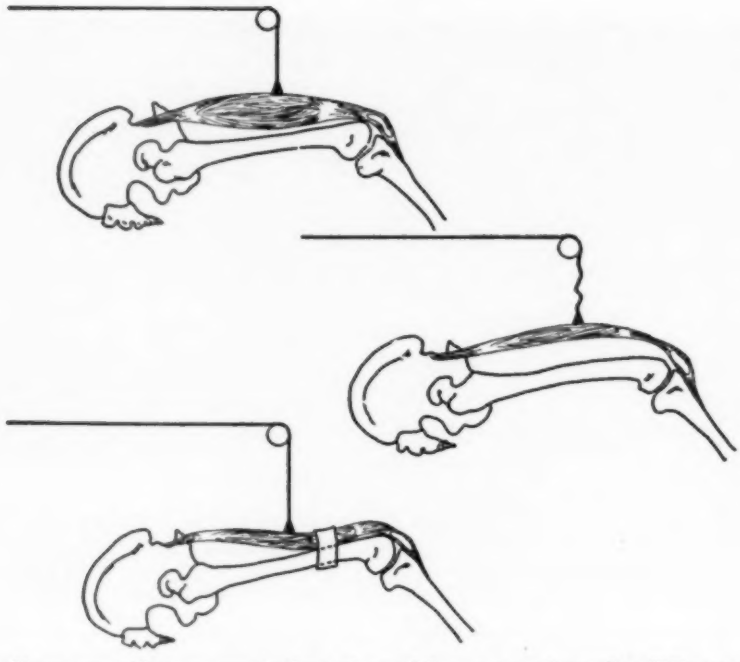

FIG. 3. A diagrammatic representation of quadriceps muscle under different conditions. *Upper*—Normal muscle likened to a rope over a pulley, with no slack, ready to lift a weight. *Middle*—Elongated atrophied muscle is comparable to a rope-pulley arrangement in which the rope is slack. *Lower*—Slack in the muscle is taken up by binding an elastic roller bandage around the thigh.

the rope. Even a weak atrophied muscle will exhibit increased strength when the slack has been eliminated by a tightly applied bandage (6).

A second experiment can be performed with the aid of a hand dynamometer (Fig. 4). Any average person with normal muscles who squeezes a dynamometer as firmly as possible, then relaxes momentarily and squeezes again, will find it impossible to reach or exceed the first effort. In fact, if the activity is continued, there will be a steady downward gradient to the point of complete fatigue. A patient with fibrositic symptoms in the hands will have the same experience, though registering a subnormal initial pressure. On the other hand, when the investigator firmly compresses the muscles of the patient's forearm with the thumb and forefinger, approximately four finger-breadths above the wrist prior to the second squeeze, the initial pressure will not only be reduplicated but exceeded by an average of 5 pounds. However, from this point on, with repetition of the motion, there will be a progressive decrease in the strength of the contractions. In Figure 4 an elastic roller bandage has been applied to take up the slack in the muscles (6).

The preceding description and explanation of the production of fibrositis indicate the reason why this term is a misnomer. Neither fibrous tissue nor inflammation appears to be involved; but rather overworked or atrophied muscle tissue. Therefore fibrositis, probably better described as "muscular rheumatism," should no longer be considered a disease of unknown etiology. It should be re-

FIG. 4. When there is atrophy of muscle in the forearm, a binder permits more vigorous contraction of the weak muscle, as registered on the hand dynamometer.

garded as a separate entity, even when the symptom complex is found in conjunction with various types of arthritis.

DIAGNOSIS

The symptoms of muscle atrophy are chronic stiffness and aching after inactivity, whether related by the patient to muscles or to joints (7). When such a joint is alleged to be stiff and aching when at rest in comparison with the contralateral member, careful examination and measurement of the motor muscles will reveal atrophy, decreased strength and loss of tonus. Frequently, abnormal hypermobility can be demonstrated.

The diagnosis of fibrositis should be suspected when aching and stiffness after inactivity (jelling) are complained of, irrespective of additional symptoms. The jelling phenomenon can be differentiated from actual pain in the joint, such as that due to an arthritis, since the latter occurs and becomes more severe when the joint is made to function. Arthritis of any type is usually associated with some chronic fibrositis due to the limited activity occasioned by the pain. For example, in a patient who complains of stiffness and aching in a joint, if x-ray examination reveals some marginal spurs and narrowing of the joint space, a diagnosis of osteoarthritis will often be made. Yet a cure can be obtained with no therapy except that directed toward reconditioning the muscles associated with the involved joint. Nevertheless, the patient has been branded with, and usually retains, the unwarranted label of "arthritic."

Fibrositis has been regarded as a psychogenic type of disability. It can be readily differentiated from psychogenic rheumatism, in which there is a bizarre anatomic distribution of complaints and a characteristic symptom pattern. In psychogenic rheumatism, salicylate and heat therapy are valueless and benefit from mild activity is questionable. Symptoms are often forgotten during the time that a person with psychogenic rheumatism is enjoying either an active or sedentary diversionary pursuit, but afterward payment is exacted for this lapse into pleasure by increased disability.

TREATMENT OF ACUTE FIBROSITIS

Acute fibrositis is generally of short duration, even if untreated. Applications of heat for twenty minutes or more, one to three times daily, and administration of salicylates will relieve the discomfort. The patient should be advised to resume normal or nearly normal activity without delay, and with as little pampering of the part as possible. If the exercise which resulted in overuse of the muscle is to be continued, the patient should be encouraged to train the muscles so that they will become adapted to the increased physical exertion.

TREATMENT OF CHRONIC FIBROSITIS

The traditional treatment of fibrositis has consisted of salicylates and physical therapeutic measures. A program of this type can accomplish gradual, and frequently limited, rehabilitation of muscles over the course of many months (Fig. 1). The modern tri-directional attack, involving relief of symptoms, improvement of function and elimination of cause, can cure chronic fibrositis in a matter of weeks (Fig. 1).

Relief of pain

The aching pain is relieved partially or completely with salicylates or analgesic combinations. The patient is not promised complete relief. The medication is given every four hours during the first several weeks of therapy, whether the patient feels the need for it or not. Much greater success will be gained from the exercises if pain is mild or nonexistent. Enteric-coated (six- to eight-hour) sodium salicylate taken seven to nine hours before arising in the morning will often enable the patient to start the day with less difficulty. There should be no need for narcotics or systemic steroid therapy in the treatment of fibrositis.

Heat from an infra-red lamp or a heating pad applied for twenty minutes or more, one to three times a day, is soothing and aids in the relief of pain and stiffness. Massage is likewise comforting. These measures can not be used as a substitute for exercises, as they in no way rehabilitate muscle.

The most recent adjunct in the treatment of fibrositis is the infiltration of steroid suspensions into the most painful area(s) (8). Hydrocortisone acetate suspension[1] (25 mg./cc.), hydrocortisone tertiary butylacetate[2] (25 mg./cc.),

[1] Hydrocortone Acetate Suspension, Merck Sharp & Dohme Research Laboratories, West Point, Pa.

[2] Hydrocortone-T.B.A. Suspension, Merck Sharp & Dohme.

and prednisolone tertiary butylacetate[3] (20 mg./cc.) have been helpful. Any one of these preparations may be used alone, or the first and second or the first and third may be used in combination. The more insoluble tertiary butylacetates do not provide relief of pain for twelve to twenty-four hours, whereas the slightly more soluble hydrocortisone acetate will usually be effective within six to eight hours. The volume to be injected varies between 1 and 3 cc., depending upon the area to be infiltrated. A combination of 1 to 2 cc. of 1 per cent hexylcain hydrochloride[4] (a relatively long-acting local anesthetic), 1 cc. of hydrocortisone acetate, and 1 to 2 cc. of one of the tertiary butylacetate suspensions will often provide continuous relief of pain from the time of injection. The duration of benefit varies between five and fourteen days—occasionally longer. There has been no evidence of systemic effect from this therapy, even when several areas are treated. Infiltration with these steroid preparations permits more rapid rehabilitation and less need for other therapy for relief of pain (8).

Improvement of function

Stiffness, which limits muscle function after arising for minutes to hours depending upon the severity of the atrophy, can be overcome rapidly in most patients by the administration of the newer muscle-relaxing drugs, *e.g.*, meprobamate[5] or zoxazolamine[6] one tablet four times a day (9–12).

A rapid forward step in treatment as well as an aid in enlisting the cooperation of the patient consists of mechanical elimination of the slack in the atrophied muscle by means of a firmly applied elastic bandage. This immediately improves function and decreases the fatigue. At the knee, the bandage may be applied in the form of a figure-of-8, or simply as a tight binder three or four finger-breadths above the patella; in the forearm it may be applied as a binder approximately four finger-breadths above the wrist. In the latter case, gauze or sponge rubber is needed as a padding to prevent undue pressure over the arteries of the forearm.

Elimination of cause

Chronic fibrositis can be cured in a relatively short period of time if the treatment is individualized and cooperation of the patient is secured (6). Most patients will do their part if they understand the need for their participation in a program of rehabilitation. This is accomplished by giving them a sufficiently complete but logical explanation of the cause of their muscle atrophy (disuse, decreased use or strain) and the relationship to the symptoms of chronic fibrositis. They should be assured that this is a curable rheumatic disease and not the first stage of a severe crippling arthritis.

Exercises for rehabilitation of muscle should be carefully taught. They must be carried out *in addition* to the usual daily physical activity. Motion of the joint is not necessary. Each contraction of the muscle should be as firm or com-

[3] Hydeltra-T.B.A., Merck Sharp & Dohme.
[4] Cyclaine, Merck Sharp & Dohme.
[5] Miltown, Wallace Laboratories, New Brunswick, N. J.
[6] Flexin, McNeil Laboratories, Philadelphia, Pa.

plete as possible. This is achieved by weighting the muscle, or exercising it against resistance. When the fibrositis involves the area of the extremities and buttocks, the initial exercises for muscle training should be conducted ten times every waking hour; after a week, they are increased to ten times every half hour. When fibrositis involves the area of the shoulders or torso, two to four different exercises performed ten times four times a day will rehabilitate the muscles. These limits are placed on the number of muscular contractions during each session in order to prevent fatigue.

All activity, whether "business as usual" or a rehabilitation program, must stop short of fatigue. Up to the point of fatigue, function may be considered as maintenance or muscle-building activity. When the fatigue threshold is exceeded, there is loss of muscle strength which, if persistent, can produce further muscle atrophy. All muscle, normal or abnormal, will function more efficiently when fatigue is avoided. Conscious regulation of activity is extremely important in the treatment of fibrositis.

Regulation is achieved by instructing the patients to stop activity *before* becoming tired and to take a thirty-minute period of complete relaxation, either sitting or reclining. The short rest period permits the muscles to recover from the previous exertion and to be ready to function efficiently again. This type of regulation is in contradistinction to the usual modern pattern of physical activity to the point of fatigue, and even to exhaustion. When atrophy is moderate to severe, the rest periods may be required frequently throughout the day, until rehabilitation of the muscles is successful.

To correct poor posture the abdominal and paravertebral muscles must be strengthened by exercises carried out four times a day. Good posture is achieved while standing or sitting if the anterior abdominal wall is retracted without other conscious physical effort. A new posture habit must be substituted for the old, long-standing one. This is best accomplished by teaching the patient an association of ideas which will recur frequently throughout the day. For instance, the homemaker is told to draw in the abdominal wall every time she walks through a doorway; or the person who works at a desk is instructed to pull in the abdominal muscles every time he picks up a pen or a pencil, as well as when walking through doorways. Some association of ideas can be worked out for every occupation. Only by constant repetition can a new posture habit become automatic and effective.

COMMENT

Fifteen years ago, a survey of our records on 500 patients with various rheumatic conditions revealed that in 65 (13 per cent) the diagnosis was fibrositis. In a similar survey just completed, fibrositis was found in 155 instances (31 per cent). In the latter group, two thirds of the cases had been previously diagnosed as some form of arthritis, although no symptoms other than those of fibrositis were present.

Some of the increase in the number of patients with "muscular rheumatism" is due to better diagnosis, but the greater part is an actual upward trend in the

frequency of occurrence. The population of the United States is becoming more sedentary, more dependent upon wheels for motion, and consequently more physically unfit. Although we lionize the athlete, the record-breakers are few and far between. Coaches of contact sports no longer find it necessary to limber highly trained muscles for several weeks to get better timing; they cautiously train inadequate muscles for a month to tighten lax joints and prevent injuries.

Our idolatrous worship of the wheel is being communicated to the younger generation to such an extent that the former U. S. Director of Physical Fitness under the Civilian Defense Program in World War II felt impelled to report in a nonscientific periodical that "57.9% of American youngsters failed in one or more six basic strength and flexibility tests, whereas only 8.7% of the European children failed them" (Kraus-Weber tests) (13). In like manner, following the "Report to the President of the United States on the Annapolis Conference on Fitness of American Youth", a White House Executive Order began "Whereas recent studies, both private and public, have revealed disturbing deficiencies in the fitness of American youth. . . ." (14).

A study of the age of patients with uncomplicated fibrositis fifteen years ago, indicated that 86 per cent were over the age of 40 as compared with only 58 per cent at the present time. It is no longer unusual to see a patient in the 30–39 year age group in whom fibrositis is severe enough to require medical treatment.

This trend should be considered alarming, particularly if the traditional concepts of etiology and therapeutics prevail. Fibrositis, in a more sedentary population, will be neither self-limited nor non-crippling. Atrophy, weakness and spasm of muscle are more contributory to the crippling effects of the various forms of arthritis than are the lesions in the joints.

In chronic fibrositis, traditional treatment with salicylates and physical therapy provides symptomatic relief and permits gradual rehabilitation of the involved muscles (many times to a limited degree) over a course of many months (Fig. 1). Active rehabilitation of muscle, in conjunction with the therapeutic program briefly outlined in this paper, can accomplish a cure within a matter of weeks. However, the task is much more difficult today, since patients must be "sold" the concept of activity in contradistinction to the heresy which they now espouse—don't walk if you can ride; don't stand if you can sit; don't sit if you can recline; and if you get urge to exercise, lie down until it passes off. Fibrositis should be prevented by rejecting ill-conceived traditional beliefs and at the same time encouraging practical physical conditioning for persons of all ages. Fibrositis should be recognized when it does occur, either alone or with other rheumatic conditions, and up-to-date therapeutic measures should be applied for relief of symptoms, improvement of function and elimination of the cause. As physicians, our responsibility lies in the prevention, diagnosis and modern therapy of this disorder.

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Abstracts of Current Literature

A SUSTAINED-RELEASE BELLADONNA PHENOBARBITAL COMBINATION IN THE TREATMENT OF GASTROINTESTINAL DISORDERS.

Backenstoe, G. S. *Pennsylvania M. J.* **60:** 983 (Aug.) 1957.

A sustained-release preparation containing belladonna alkaloids and phenobarbital was used over a two-year period in the treatment of 64 patients with gastrointestinal and cardiovascular disorders and with symptoms of stress. The conditions present and the numbers of patients affected were: ulcer or ulcer syndrome, 10; other gastrointestinal dysfunction, 13; cardiac and/or vascular disease, 10; stress syndrome, 20; rheumatic disease, 3; bronchiectasis, 1; migraine with stress, 2; hypothyroidism with stress, 2; chronic sinusitis with stress, 2; and anemia with stress, 1. The response was judged purely clinically by the degree of relief of symptoms and the severity or mildness of side-effects accompanying the use of the medication. An excellent response was obtained in 35 patients, a good response in 8, a fair response in 3, and a poor result in 12. Three patients were dropped from the series and 3 others required other therapy. Dermatitis, dizziness with diarrhea, drowsiness, and dermatitis with tachycardia occurred as side-actions in 1 patient each. The preparation was well accepted by the patients. The convenience of its administration once daily proved advantageous. The patient could depend upon quiescence of his symptoms for eight to ten hours, and therefore was able to relax and overcome tension. Because of its success in counteracting the symptoms of parasympathetic stimulation, it is concluded that this sustained-release belladonna-phenobarbital preparation is of value as a supportive medication in patients with gastrointestinal and cardiovascular disorders.

THE PROBLEM OF CORONARY ARTERY DISEASE.

Beck, C. S. Program, *10th Ann. Meeting, Gerontological Society, Inc.*, Cleveland, October 31— November 2, 1957.

When a coronary artery is occluded, the fate of the patient depends upon the amount of blood that reaches ischemic muscle. Quantities of blood in the range of several cubic centimeters per minute make an important difference in determining what happens after an artery is occluded. One of the two things that can happen is due to the changes in oxygen content between ischemic muscle and well oxygenated muscle. This checkerboard distribution of oxygen produces anginal pain, electrical instability, and currents that may be strong enough to cause fibrillation of the heart. The other reaction produced by occlusion is death of muscle. These two reactions should be distinguished one from another, because they produce different types of death and yield to different forms of treatment. Most of the fatal heart attacks are due to differences in oxygen content in the heart muscle. The total coronary inflow in most of these instances is adequate to maintain the heart beat, but because the blood is not evenly distributed throughout the heart muscle, fibrillating currents are produced and these kill. Surgical operation can bring about a more even distribution of blood which enters the heart through the diseased blood vessels. This operation does not add blood from outside sources; it distributes the blood that is there so that it can be utilized in a more effective way. The operation accomplishes this by producing intercoronary channels. These are connections between one small artery and another so that a red cell, once it enters the coronary circulation, can go anywhere within the heart's substance that it can do the most good. The operation consists of mechanical abrasion of the lining of the parietal pericardium and the surface of the heart, the application of a mild inflammatory agent in the form of powdered asbestos to the surface of the heart, narrowing of the coronary sinus, and the application of the peri-

cardial fat to the surface of the heart. The experimental background for the operation consists of about 6,000 operations on dogs' hearts over the past twenty-five years. The operation has a sound physiologic basis and these physiologic facts will remain. The results in patients are good. Almost every patient is either completely relieved of pain or has a significant reduction of pain and is able to return to work. The operation has limitations in that it does not cure the disease, but at present it is the most effective treatment for coronary artery occlusion and angina pectoris. In the last 178 consecutive patients operated upon there were 2 operative mortalities. A recent editorial in *Lancet* states that there is "a good case for giving the operation an extensive trial, and results so far offer grounds for sober optimism."

COMBINED THERAPY FOR PEYRONIE'S DISEASE.

Burford, E. H., and Burford, C. E. *J. Urol.* **78:** 265 (Sept.) 1957.

Among 186 patients with Peyronie's disease reported, 87 per cent were between the ages of 40 and 69 years. The average age of the entire group was 53 years. Sixty-one patients (33 per cent) gave a history of trauma as the probable etiologic factor in the disease. The lesions averaged 2 by 3 cm. in size. The presenting symptom had been present an average of 8.2 months, the maximum duration being 132 months and the minimum duration two weeks. Among the 151 patients for whom the duration of symptoms could be determined, 54 per cent reported to the urologist within six months and 91 per cent by the end of one year. One hundred and thirty-four patients were treated, 4 with ultraviolet rays, 96 with radium plaque, 1 with radium plaque and radon, 31 with radium plaque and Tocopherex (mixed tocopherols), and 2 with Tocopherex alone. The average exposure to the radium plaque was 120 mg.-hours for a single treatment. The number of treatments was two in 32 patients, four in 3, five in 4, and five, seven, and eleven in 1 patient each. Tocopherex was given in a dosage of one 50-mg. capsule daily for thirty to sixty days. Complications consisted of an indolent weeping ulcer at the site of application of radium in 3 cases. Two ulcers were successfully excised but skin grafting was required in the third patient. The use of the radium plaque alone and supplemented with Tocopherex yielded the best results, with cure or improvement rates of 77 and 84 per cent, respectively. Small, repeated exposure to the radium plaque is the preferred method of therapy. It is advised that all patients be followed for at least two years before their final status is determined. Treatment of the same lesion may safely be repeated in eight months.

ACUTE PANCREATIC LESIONS IN PATIENTS TREATED WITH ACTH AND ADRENAL CORTICOIDS.

Carone, F. A., and Liebow, A. A. *New England J. Med.* **257:** 690 (Oct. 10) 1957.

Tissue sections of pancreas obtained at necropsy from 54 consecutive patients treated with ACTH or adrenal corticosteroids, including cortisone, hydrocortisone, prednisone, and prednisolone were studied. Control material consisted of similar sections from 54 patients of similar age and with comparable diseases. Evidence of acute pancreatitis or fat necrosis or both was found in 16, the changes being mild in 6, moderate in 7, and severe in 3 instances. Pancreatitis alone was present in 4 cases and fat necrosis alone in 3. Both lesions were present in 9 cases. In the control series, 2 cases of acute pancreatitis without fat necrosis were found. In 2 additional steroid-treated patients, focal small zones of organized fat necrosis were found. One of these had received large doses of ACTH and cortisone seven months previously, and the other had been receiving cortisone treatment for more than five months at the time of death. This was interpreted to indicate that steroid-induced changes in the pancreas are not necessarily progressive but may subside and heal. Ectasia of pancreatic acini occurred in 32 (59 per cent) of the steroid-treated patients and in 13 (24 per cent) of the control patients. Among the former, the changes were mild in 16, moderate in 12, and severe in 4, whereas in the control group the lesions were mild in 12 cases, and moderate in 1. It is postulated that adrenal steroids may alter pancreatic

secretion and produce obstructive acinar changes with release of pancreatic enzymes. Sections of the pancreas showed no evidence of fat embolism. No diffuse or hemorrhagic pancreatitis was seen. The patients with pancreatic lesions had no signs or symptoms of pancreatitis, but some of them had abdominal distress and episodes of vomiting and fever while receiving steroid therapy. Severe acute infections occurred in 15 of the 16 patients with pancreatitis or fat necrosis, and bacteremias were demonstrated in 4 of them. However, in view of the fact that cortisone, in the absence of infection, experimentally can produce changes in the pancreas similar to those observed in the patients in this treated group, it is concluded that bacterial infections probably played a secondary part, if any, in the pathogenesis of the lesions. Short courses of adrenal corticoids to combat hypotension or overwhelming toxic effects during the destructive phase of severe acute pancreatitis probably would cause no further destruction, but these steroids should not be employed for prolonged periods in this disease because of the possibility of injury as described here.

PENTOLINIUM-MEPROBAMATE THERAPY. THE OLDER PATIENT WITH HYPERTENSION. Fulton, L. A.; Williams, B., and Barker, A. *Am. Pract. & Digest Treat.* **8:** 1376 (Sept.) 1957.

The problem of whether or not the elderly patient with elevated blood pressure should receive specific hypotensive medication was attacked by reasoning that, since essential hypertension frequently is a sequel to stress in daily living, the use of a medication that would facilitate emotional adjustment would prove helpful. A study was conducted with 24 elderly patients (two-thirds of them between the ages of 60 and 86 years) who had had significant hypertension for thirty years or more and all of whom complained of the typical subjective symptoms. Four patients received meprobamate alone, 1 patient pentolinium alone, and 19 patients the two drugs in combination. The average dosage of pentolinium was 40 mg. three times daily, and the highest dosage 100 mg. three times daily (which 2 patients received). The dosage of meprobamate was standardized at 400 mg. three times daily. The duration of treatment varied from one and one-half to ten months. Among the patients who received pentolinium, there occurred a fall in systolic blood pressure of 40 mm. Hg or more in 70 per cent, a fall of 25 mm. Hg or more in diastolic pressure in 40 per cent, and no significant reduction in either in 20 per cent. One patient in the latter group had chronic nephritis with renal hypertension. Two of the 4 patients who received only meprobamate experienced a significant reduction in both the systolic and diastolic pressures and simultaneously had symptomatic relief. The most significant result of combined therapy was the relief of headache, dizziness, palpitation, tinnitus, epistaxis, nervousness, and insomnia, and of angina pectoris in 1 patient with aortic insufficiency. No evidence of sensitivity, chronic toxicity, or tolerance to meprobamate became apparent nor any disturbing side-effects of ganglionic blockade. This study led to the conclusions that elderly patients may be more susceptible to the action of ganglionic blocking agents than younger persons, and that the tranquilizing action of meprobamate on the central nervous system, with consequent release of muscular tension, may combine with the hypotensive action of pentolinium in small dosage to produce a more pronounced decrease in blood pressure than might be expected from the same dosage of the ganglionic blocking agent alone. Pentolinium appears to have a place in the treatment of elderly persons with hypertension. Further study of meprobamate as an adjunct in the antihypertensive regimen is warranted.

THE USE OF PREDNISONE IN CONGESTIVE HEART FAILURE. Gutner, L. B.; Moses, J. B.; Dann, S., and Kupperman, H. S. *Am. J. M. Sc.* **234:** 281 (Sept.) 1957.

A study was conducted in 11 patients with congestive heart failure of the action of prednisone upon sodium, potassium and water excretion. Eight of the patients were main-

tained in compensation through the daily use of digitalis. Three periodically required, in addition, mercurial diuretics parenterally. The patients were observed during a control period and then received 20 mg. of prednisone daily for one week. At this time, the laboratory determinations were repeated and then the dosage was increased to 40 mg. daily for another week. The tests were repeated after this interval. Prednisone was found to have a favorable effect upon the status of these patients. Dyspnea decreased in 5 patients; 3 of these also lost weight, 1 gained weight, and 1 remained unchanged. Prednisone had no deleterious effect upon the status of another 5 patients who were well compensated; body weight remained constant in 3 of these patients and decreased in 2. One patient in the series had some increase in exertional dyspnea associated with a gain in weight that was accompanied by a marked increase in appetite. A decrease in 17-ketosteroid excretion followed the use of prednisone in 8 patients. It was unaffected or showed a variable response in the other 3. This was interpreted as evidence of the suppression of endogenous ACTH secretion with secondary adrenal depression. The 24-hour urinary excretion of sodium was increased in 7 patients, decreased in 2, and showed a variable response or remained unchanged in 2 patients. Prednisone had a similar effect upon the excretion of potassium. The steroid had no effect upon blood pressure in 7 patients. The readings were lowered in 2 patients and variable in 1 other. The systolic pressure in 1 patient rose. It is concluded that prednisone may safely be administered to patients with congestive heart failure. The possible mechanisms of its action are discussed.

TOLBUTAMIDE IN THE MANAGEMENT OF THE ELDERLY DIABETIC PATIENT.

Hamwi, G. J. Program, *10th Ann. Meeting, Gerontological Society, Inc.*, Cleveland, October 31–November 2, 1957.

Experiences in treating approximately 150 patients with Tolbutamide show that this compound is most effective in the older, milder diabetic patient. Its obvious advantages are its hypoglycemic activity, the fact that it is a sulfonamide derivative and therefore one of a class of compounds of which the undesirable side-actions have received prolonged study, the relative paucity of severe hypoglycemic reactions during its use, its relatively slight toxicity, and the convenience of its administration orally. The disadvantages of the use of Tolbutamide are the lack of ability to predict its effectiveness in any one patient, its ineffectiveness in the presence of acidosis or severe stress, the possibility of minimizing the importance of dietary control by substituting therapy with Tolbutamide, the theoretic possibility that lowering the blood sugar by itself may be inadequate to prevent other associated metabolic derangements, and the unknown potential effect of this compound upon the control or production of chronic degenerative vascular complications.

THE EFFECT OF PAGET'S DISEASE UPON THE CARDIOVASCULAR SYSTEM.

Hultgren, H. N., and Caul, E. Program, *10th Ann. Meeting, Gerontological Society, Inc.*, Cleveland, October 31–November 2, 1957.

Paget's disease has been alleged to involve the cardiovascular system by an increased incidence of calcific valvular disease, an increased cardiac output, and an excessive degree of arteriosclerosis. Observations supporting these contentions, however, are scanty. Therefore a study was made of 121 patients with severe, generalized Paget's disease, and of 417 control patients in a similar age group who were not affected by the disease. Necropsy findings in 27 patients were compared with similar data from two control groups—a series of 201 patients in the same age group and 50 unselected patients who were beyond 80 years of age. The following observations were made: 1) Grossly visible calcification of the mitral and aortic valves was present in 59 per cent of 27 cases of severe Paget's disease that came to necropsy, compared to an incidence of 18 per cent in 201 control cases in the same age group, and 40 per cent in patients over 80. The incidence of significant calcific aortic stenosis in the three groups was 31 per cent, 7.5 per cent, and 10 per cent, respectively. 2) Clinically evident aortic stenosis was present in 21 per cent of 66 patients with severe Paget's

disease whose clinical records were reviewed, compared to an incidence of 4 per cent in 417 control patients. 3) An analysis of blood pressure, pulse rates, calculated cardiac outputs (Starr formula), and heart weights from patients with severe Paget's disease revealed no deviation from similar data obtained on control subjects. 4) Clinical manifestations of arteriosclerosis such as cerebrovascular accidents, angina pectoris, or myocardial infarction were no more frequent in patients with Paget's disease than in control patients. The incidence of coronary and aortic arteriosclerosis was similar in the two groups. It is therefore concluded that the principal effect of severe Paget's disease upon the cardiovascular system is the development of an increased incidence of calcific valvular disease involving both mitral and aortic valves resulting in a striking increase in the incidence of clinically significant aortic stenosis. In addition, these data provide further support to the concept that aortic stenosis in the elderly may be of nonrheumatic origin.

MOTOR COMPLICATIONS OF HERPES ZOSTER.

Kendall, D. *Brit. M. J.* **2:** 616 (Sept. 14) 1957.

Fourteen cases are described in which the patients suffered paralysis as a result of herpes zoster infection. The distribution of the paralysis varies greatly but corresponds approximately to the distribution of the rash. It is now generally accepted that herpes is essentially an affection of the central nervous system rather than of the dorsal root ganglia, thus making the not infrequent appearance of motor symptoms more logical. It is suggested that a certain number of patients with "Bell's palsy" may, in fact, be suffering from the Ramsey-Hunt syndrome, and the points of similarity between zoster paralysis in the upper limbs and the clinical condition described as neuralgic amyotrophy are such that there may be grounds for considering the two conditions etiologically similar. The prognosis in zoster paralysis is on the whole good, but the incidence of recovery from facial paralysis due to this cause is not as satisfactory as in true Bell's palsy. Recovery of paralyzed limbs is usually nearly complete. (From author's summary.)

THE CONTROL OF FATIGUE IN THE AGED.

Klumpp, T. G. *Connecticut State M. J.* **21:** 912 (Oct.) 1957.

Fatigue, the most prevalent limiting factor in the lives of older persons, can often be controlled. This requires a painstaking analysis of the patient's physical, mental and emotional status to rule out specific diseases and dysfunctions, to discover unhygienic patterns of living, and to determine whether emotional conflicts are the basis. In the absence of a specific disease, fatigue in older persons arises principally from: 1) diminution of organic reserve, particularly of the heart and circulation due to loss of vascular elasticity and arteriosclerosis; 2) decline of endurance of mental and emotional effort, the basis of which is the compounding of the organic changes in the central nervous system that accompany the aging process; 3) atrophy of disuse; 4) loss of incentive, motivation and interest; and 5) decline of endocrine activity. The alleviation of fatigue consists of shrinking the patient's activities to the point where fatigue disappears, or instituting measures that will tend to enhance endurance and tolerance, and realizing that rest is not a universal panacea for fatigue. Physiologic principles that apply here should be borne in mind, such as the fact that functional capacities are maintained only through use; these capacities can be augmented, within limits, only through repeated stress; the atrophy of disuse commences rapidly and capacities that are relinquished are soon lost; functional capacities decline with age, but they decline less rapidly if they continue to be used. The most effective approach lies in preventing fatigue through maintaining an adequate neuromuscular reserve against stress. Some degree of reserve can be regained, provided its loss is not due to advanced organic disease, through a regimen of graded exercise. This means finding some physical activity that will be enjoyed and continued voluntarily by the patient. The patient should sleep well at night. If emotional disturbances interfere, a somnifacient may be prescribed. Mental and emotional fatigue, as at the end of a trying and sedentary day,

can best be overcome by physical activity. Fatigue in persons who are overweight requires adherence to a proper dietary regimen, and stress upon the importance of exercise. Estrogens and androgens may be of benefit in older persons in whom endocrine deficiencies contribute to fatigue. If the basal metabolic rate is low, desiccated thyroid may sometimes be helpful. Sympathetic amines may be used on occasion to counteract fatigue. They are best administered in conjunction with a small dose of a sedative to overcome their tendency toward causing nervousness and sleeplessness. No reliable correlation exists between how hard a person works and the degree of fatigue experienced. Fatigue is most likely to occur in elderly persons who have too little to do. A new and absorbing interest must be found in order to give them a new lease on life.

UEBER DAS VERHALTEN DER HYDROXYINDOLESSIGSÄURE-AUSSCHEIDUNG IM URIN NACH RESERPIN BEIM MENSCHEN: MIT BESONDERER BERÜCKSICHTIGUNG DES KARZINOIDSYNDROMS. (THE URINARY CONTENT OF HYDROXYINDOLACETIC ACID FOLLOWING RESERPINE IN MAN, WITH SPECIAL REFERENCE TO THE CARCINOID SYNDROME).

Langemann, H., and Goerre, J. *Schweiz. med. Wchnschr.* **87:** 607, 1957; through Ciba Literature Review **2:** 219 (July) 1957.

In metastatic carcinoid of the small intestine, large amounts of serotonin are present in the tumor tissue and the blood serotonin level may be considerably increased. A degradation product of serotonin is hydroxyindolacetic acid which is excreted in the urine. Animal experiments have shown that large doses of reserpine reduce the hydroxytryptamine concentration. The concentration of hydroxyindolacetic acid in the urine increases at the same time. In order to investigate the other effects of hydroxytryptamine in man, the authors examined in a fairly large series of tests whether and how the excretion of hydroxyindolacetic acid is changed in patients receiving reserpine. This excretion is, as a rule, considerably increased in cases of carcinoid syndrome. The authors studied the question of whether Serpasil is capable in such cases of provoking an increase in the excretion of hydroxyindolacetic acid, which in any case far exceeds that of noncarcinoid patients, and whether this circumstance could be used for diagnostic purposes. Following the administration of Serpasil (0.5 to 2.5 mg. intravenously), the excretion of hydroxyindolacetic acid failed to increase appreciably in noncarcinoid patients. When a carcinoid syndrome was present, however, it rose considerably. It is possible that this phenomenon may serve as the basis for a provocative test and thus lead to the early detection of the carcinoid syndrome.

VAGINAL CYTOLOGY IN BREAST CANCER PATIENTS.

Liu, W. *Surg., Gynec. & Obst.* **105:** 421 (Oct.) 1957.

The vaginal cytology of breast cancer patients was found not to differ significantly from that of control patients. The exfoliated cornified cells and basal cells were similar in the two groups. Vaginal cytology proved of no assistance in selecting patients for castration, in predicting the clinical response following castration, or in selecting patients for hormonal therapy. However, vaginal cytology could be used to good advantage in following patients with breast carcinoma during treatment with estrogens and androgens. A correlation between a favorable clinical response and a marked hormonal effect cytologically was found, as well as a correlation between refractoriness to a hormone clinically and an insignificant hormonal effect upon the vaginal smear. This observation was particularly clear in the case of patients treated with estrogens. It was concluded that a full hormonal effect as shown by the vaginal smear is a prerequisite for a clinical remission. For this reason, repeated vaginal smears should be performed during hormonal therapy for breast cancer, along with gradually increased dosage, in order to arrive without delay at a dosage level that is optimal and effective in individual patients.

INCIDENCE OF MEGALOBLASTIC ANEMIA AFTER SUBTOTAL GASTRECTOMY.

MacLean, L. D. *New England J. Med.* **257:** 262 (Aug. 8) 1957.

By means of the absorption of radioactive vitamin B_{12} as an assay for intrinsic factor in 13 patients who at least three months previously had undergone various types of subtotal gastrectomy, 1 patient was found who failed to absorb the vitamin. Upon histologic examination of the resected portion of stomach, atrophy typical of pernicious anemia was observed, along with intestinalization of the mucosa and round-cell infiltration. Thereafter, it was found that all patients in whom megaloblastic anemia followed partial gastrectomy performed at one institution between the years 1938 and 1950 (9 of 1550 patients operated upon) demonstrated the same typical changes when the previously resected stomach was examined. Apparently, patients who are capable of producing adequate quantities of intrinsic factor when the stomach is intact may become deficient in this capacity if the stomach is partially resected. It is believed that the development of megaloblastic anemia after partial gastrectomy can be predicted by the results of microscopic examination of the resected portion of stomach.

EFFECT OF DIVISION OF THE TESTICULAR ARTERY ON VIABILITY OF THE TESTIS IN MAN.

Maluf, N. S. R. *J. Urol.* **78:** 437 (Oct.) 1957.

The testicular artery was divided bilaterally in 3 elderly patient volunteers, as the "first stage" of orchiectomy for metastatic adenocarcinoma of the prostate gland. The histologic appearance of the testis and the 24-hour urinary output of 17-ketosteroids showed no essential change after division of the testicular artery. Division of the spermatic cord proximal to the external inguinal ring and of the vas deferens and its vessels in 1 middle-aged patient resulted in abolition of spermatogenesis in one testis and infarction in the other testis, followed by fibrosis. Division of the testicular artery to an atrophic undescended testis in a 23-year-old man did not obliterate the entire arterial supply to that testis. It is concluded that it would be permissible to divide the testicular artery in the abdomen if a surgical advantage could be gained. Testicular atrophy from such a procedure would be unlikely. The pertinent literature is summarized. (From author's summary.)

THYROID PATTERNS. THEIR IDENTIFICATION AND MANAGEMENT AFTER AGE SIXTY-FIVE.

McGavack, T. H., and Seegers, W. Program, *10th Ann. Meeting, Gerontological Society, Inc.*, Cleveland, October 31— November 2, 1957.

A study has been made of the thyroid and its function in more than 600 patients in a chronic disease hospital and home. The subjects ranged in age from 44 to 99, with between 90 and 95 per cent over the age of 60, and from 20 to 25 per cent over the age of 80. Approximately equal numbers of the two sexes were included. Various clinical and laboratory parameters of thyroid function have been oriented in relation to the physical characteristics of the thyroid gland. Of the women surveyed, approximately one-eighth had normal glands, less than 3 per cent diffusely enlarged glands, and from 3 to 5 per cent enlarged nodular thyroids. In about one-fourth, the gland was small; in slightly less than one-fifth, one lobe only was palpable; and in 35 to 40 per cent, the gland was not palpable. One striking difference was seen in men, namely, that in nearly two-thirds of them, the gland was not palpable. The uptake of I^{131} by the thyroid varied from 3 to 40 per cent, with an over-all average of 20.0 per cent (men) and of 20.4 per cent (women) in those patients over 60 years of age. The serum protein-bound iodine values varied from 2.4 to 9.1 micrograms per 100 cc., with an over-all average of 6.17 micrograms per 100 cc. In none of the cases were there overt signs of hyperthyroidism or hypothyroidism. Insofar as basal metabolic rates could be established and extrapolated with existing tables, they were within normal range for each subject. Values for serum cholesterol concentration varied rather widely but bore no apparent relationship either to the physical status of the thyroid or to

the general condition of the patient. Although some of the signs commonly associated with myxedema may be seen in older people, it was not possible to correlate these directly with the foregoing parameters of thyroid function. A definite relationship seems to exist between thyroid and pelvic disturbances. The percentage of this correlation is compared with the relationship of thyroid disease to some nonspecific nonrelated condition. The functional responsiveness of the thyroid was tested in a limited number of patients by administration of TSH. Such responses can be considered normal.

EFFECT OF HYDROCORTISONE AND PREDNISONE ON THE EXCRETION OF UROPEPSIN IN RHEUMATIC SUBJECTS.

Oka, M., and Aho, J. *Acta rheumat. scandinav.* **3:** 68, 1957; through Ciba Literature Review **2:** 201 (July) 1957.

The daily excretion of uropepsin, which can be regarded as comparable to the total pepsin secretion, is constant in healthy subjects. An evaluation of some 300 uropepsin determinations performed on patients with articular rheumatism yielded the following results: When a daily dose of 40 mg. of hydrocortisone or 10 mg. of prednisone was administered for a short period, uropepsin excretion remained unaffected. When these hormones were given in double the doses, the urinary uropepsin level showed a clear-cut rise. There was no marked difference between the effect of hydrocortisone and that of prednisone. Six of 15 rheumatic patients, who had been receiving prednisone (7.5 to 15 mg. daily) for periods ranging from three months to four and a half years, complained of dyspepsia. These patients showed an hourly uropepsin excretion of 25.5 U, whereas the other 9 patients excreted only 10.2 U. The mean value for all 15 cases treated with prednisone was 16.3 U, whereas in a control group of rheumatic patients who had not received corticosteroid hormones and did not suffer from gastric disorders, the mean hourly uropepsin excretion was 12.9 U. Uropepsin excretion is thus not increased by prednisone or hydrocortisone if these hormones are given in normal therapeutic doses. It rises, however, when large amounts are used. After a specified dose of prednisone, the increase is no greater than after four times the amount of hydrocortisone.

INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY.

Thomas, E. D.; Lochte, H. L., Jr.; Lu, W. C., and Ferrebee, J. W. *New England J. Med.* **257:** 491 (Sept. 12) 1957.

Observations from a year's experience in collecting, storing and using human bone marrow are reported. Marrow was collected from fetal and adult cadavers, from ribs removed at surgery, and from aspiration biopsy of the ilium. The marrow from all sources was passed through a stainless steel screen, broken into a smooth cellular suspension, and the fat usually removed by centrifuging. The cells, resuspended in tissue-culture fluid and serum were administered intravenously or frozen in glycerol and stored at −80° C. for later use. After thawing, the osmolarity of the glycerol was reduced by the Solviter procedure. Sterility of the injection material appears to have been achieved. The sources utilized in this study have solved the problem of procurement. Based upon the effective dose in experimental animals, 4 to 40 million nucleated marrow cells of the usual differential count would appear to be the amount effective in man to produce repopulation of the marrow space in an adult after lethal radiation. The intravenous infusion of suspensions of marrow cells proved safe in 6 patients, 2 of whom had leukemia, 1 multiple myeloma, 1 a massive cerebral hemorrhage, 1 carcinoma, and 1 metastases from a primary carcinoma of unknown site. No embolic phenomena occurred and no immune reactions to foreign protein. The homograft grew in 2 cases in conformity with animal experimentation wherein a temporary "take" was found to occur after moderate irradiation, but a permanent or prolonged "take" only after sufficient irradiation to produce bone marrow aplasia. This could mean that, in certain patients with disseminated carcinoma, it might prove advantageous to expose the entire body to irradiation and to use marrow transplantation

to correct the resulting aplasia. The hazards of this procedure would be the possibilities of immediate or delayed reaction to foreign bone marrow, failure of the graft, and late sequelae of heavy radiation. The homograft failed to grow in 2 patients who received large amounts of chemotherapeutic agents toxic to bone marrow. These agents probably do not alter the immune state as does radiation, an effect which is necessary to insure survival of the homograft. Until each compound can be investigated, marrow homografts should not be considered a means for restoring hematopoiesis after toxic chemotherapy. The possibility of treatment of agammaglobulinemia with marrow transplantation is discussed. Marrow ought not to be used in this indication except as a last resort after the failure of other forms of therapy. Marrow transplantation will have wide application in patients who lack bone marrow and in those whose therapy is limited because of damage to the bone marrow. Patients with leukemia and those with uremia should receive first consideration. All such applications will lay the ground work for the use of marrow transplantation in victims of radiation disasters, should that ever become necessary.

ATHEROMATOUS EMBOLI TO THE KIDNEYS AFTER AORTIC SURGERY.

Thurlbeck, W. M., and Castleman, B. *New England J. Med.* **257:** 442 (Sept. 5) 1957.

Seventeen of 22 patients (77.3 per cent) dying after surgery or aneurysm of the abdominal aorta, or for atherosclerosis of the abdominal aorta with occlusion, had acute emboli of atheromatous material in their kidneys. Emboli were not found in patients whose aortas were smooth, but were common in patients with atherosclerotic and ulcerated aortas. Four patients had multiple renal emboli, and showed an identical and recognizable syndrome. Postoperatively, they were anuric or severely oliguric, and died in uremia. The infarcts in these patients could be dated, and occurred at the time of surgery. Each was caused by an embolus. The patients had no other acute renal disease nor any other cause for the uremia. Four other patients had a similar degree of embolization and were anuric or oliguric. They died of other causes, but it was believed that had the circumstances been different, they would ultimately have died from uremia. Among control patients not operated on, embolization of the kidneys by atheromatous material from the aorta was found in 13 of 42 patients (31.0 per cent) with large aneurysms, and in 6 of 38 patients (15.8 per cent) with severe aortic atherosclerosis, ulceration, and mural thrombosis. It is postulated that clamping and manipulation of the aorta may fragment atheromatous plaques. In the cases discussed, the clamp was applied from just below to 4 cm. below the renal arteries. There is probably considerable turbulence proximal to the clamp that tends to disturb atheromatous material, which is then carried to the nearest vessels, the renal arteries. If this be the cause, embolization should be minimized by careful handling of the aorta, and gentle but decisive clamping. Protection of the renal arteries by tapes or other means is probably too dangerous a procedure to use. Seven patients who survived aortic surgery for aneurysm were followed to determine whether hypertension would develop as a result of emboli that they probably suffered at the time of operation. No essential change in blood pressure readings occurred during follow-up periods of eight to thirty months.

COMPARISON OF THE HYPERGLYCEMIC EFFECTS OF GLUCOCORTICOIDS IN HUMAN BEINGS. THE EFFECT OF HEREDITY ON RESPONSES TO GLUCOCORTICOIDS.

West, K. M. *Diabetes* **6:** 168 (March-April) 1957.

The carbohydrate-metabolism regulating (or hyperglycemic) potency of a steroid may be quickly and easily estimated by testing the degree to which it modifies glucose tolerance (as measured by a single blood glucose determination two hours after glucose by mouth). The hyperglycemic potency of a steroid may be accurately estimated by testing only a few subjects, if they are tested to both a known and unknown steroid with similar characteristics of time-action. Using such a method, the carbohydrate-metabolism regulating potencies of oral prednisone and prednisolone were more than five times more potent than cortisone acetate in the hyerperglycemic effects. Prednisone and hydrocortisone were

identical in effect when administered orally in a dosage ratio of 1 to4. Older subjects showed a "positive" response to this steroid-glucose test more frequently than younger subjects. The strikingly similar responses of identical twins to glucose tolerance tests and to steroid-glucose tolerance tests suggest that heredity plays a significant role in conditioning the hyperglycemic response both to glucose loading and to glucocorticoids. Nondiabetic subjects with a family history of diabetes showed significantly greater hyperglycemic responses to prednisone and prednisolone-glucose tolerance tests than did a control group. The responses to prednisone-glucose tolerance testing of 14 subjects with a positive family history were no greater than the responses of subjects with a much less significant family history. These latter data are not adequate to permit a final conclusion, but suggest that the steroid-glucose tolerance test has limited ability to predict the eventual development of diabetes. Although long-term follow-up of persons who exhibit both "positive" and "negative" responses to tests is planned, it is hoped that the degree to which the responses to steroids are conditioned by diabetic heredity may be elucidated at an earlier date by using the methods resembling those described. (From author's summary and conclusions.)

MALIGNANT CHANGE FOLLOWING HERPES SIMPLEX.

Wyburn-Mason, R. *Brit. M. J.* **2:** 615 (Sept. 14) 1957.

Search of the literature revealed no mention of herpes simplex as a premalignant condition. Six cases are reported wherein a malignant change occurred following herpes simplex. In each instance, examination of a biopsy specimen showed squamous carcinoma. These lesions healed during radiation therapy. Recurrent attacks of herpes simplex preceded the malignant change in 2 patients. The herpetic lesions failed to heal, sometimes became ulcerated, increased in size, and bled. In 1 patient, exposure to sunlight caused continual breakdown of the healing of the herpetic lesion. One year after complete healing of the carcinoma in 1 patient, exposure to sunlight caused a further herpetic lesion to appear. The possibility that these cases furnish evidence for the virus theory of cancer causation is discussed. Recurrent herpes simplex appears to predispose to malignant change in elderly persons. It may be that this change is only an example of what may occur at the site of any chronic irritation or inflammation. However, the thought is expressed that, if all, and particularly recurrent, cases of herpes simplex are due to local infection with herpes simplex virus, and inasmuch as the subjects may exhibit abnormal sensitivity to sunlight (as do tar workers and those subject to x-ray or arsenical dermatitis and xeroderma pigmentosa), infection by the virus may be an important cause of malignant change.

SENILE URETHRITIS IN WOMEN.

Youngblood, V. H.; Tomlin, E. M., and Davis, Joseph B. *J. Urol.* **78:** 150 (Aug.) 1957.

Furacin urethral suppositories contianing 0.2 per cent Furacin and 2 per cent diperodon hydrochloride, a topical anesthetic, in a water-soluble base produced good results in the treatment of urethritis in premenopausal women. Senile urethritis in postmenopausal women, which in most cases appears to be due to a deficiency of endogenous ovarian hormone, did not respond. Excellent results could be obtained in the latter condition, however, with a Furacin suppository containing, in addition, 0.1 mg. of diethylstilbestrol. Treatment of 120 female patients with senile urethritis with this kind of suppository was followed, in 91 per cent, by the disappearance of endoscopic signs of urethral irritation, disappearance of senile vaginitis, diminution in size of bladder-neck polyps when present, and an increased elasticity of the urethra observed on sounding. The other 9 per cent required treatment for such conditions as caruncle, bladder-neck contracture, and cystocele. Preliminary histologic study by means of Papanicolaou stains of exfoliated cells of the urethral mucosa in 12 patients showed that a healthy stratified squamous epithelium regularly replaced the atrophic urethral epithelium after two weeks of topical therapy with Furacin and diethylstilbestrol suppositories. Nonspecific urethritis also improved during their use.

News and Notices

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Lankenau Hospital Number

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This Conference was made possible by a generous grant to Lankenau Hospital from McNeil Laboratories, Inc., Philadelphia, Pennsylvania.

Both Lankenau Hospital and McNeil Laboratories are to be congratulated upon having made possible this Conference, which has so well summed up the many problems facing our older people, and from which new answers to some of these problems may be expected to evolve.

Architect's drawing, the Lankenau Hospital group of buildings, showing the new Health Survey Building (right) now under construction as the first phase of the Hospital's $40,000,000 expansion program.